e-ISSN 2544-1620

Medical Science Pulse 2020 (14) 2

Original papers

DOI: 10.5604/01.3001.0014.2323

GENDER DIFFERENCES IN CIRCULATORY ADJUSTMENT TO HEAD-UP TILT TEST IN HEALTH

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: A tilt table test is a useful, non-invasive technique that has been used for the last few decades to detect autonomic failure. The response to tilting may vary physiologically between sexes.

Aim of the study: To assess the gender-specific changes in cardiovascular response to a tilt test in healthy subjects.

Material and methods: This experimental study was conducted on 90 healthy males and females aged 18–60 years, from 2019 to 2020. Forty-five male subjects and 45 female subjects were included. Using a motorized tilt table, a tilt table test was performed at 60 degrees for 10 minutes. An automatic sphygmomanometer was used to measure blood pressure (BP), and heart rate (HR) and a pulse oximeter was used for the measurement of peripheral capillary oxygen saturation (SpO_2). An independent sample t test, a multiple regression analysis and a chi squared test were conducted for statistical analyses.

Results: A significantly greater drop in systolic blood pressure (SBP) was observed in females, compared to males after tilting. In 5.5% of the subjects, orthostatic intolerance occurred, but there were no significant age or gender- specific differences in subjects with orthostatic intolerance.

Conclusions: This study concluded that in response to tilting, cardiovascular response was less pronounced in females.

KEYWORDS: male, female, tilt test, SBP, DBP

Background

Recurrent episodes of unexplained syncope are a common and challenging problem in clinical practice [1]. Many patients in outpatient departments complain of “blackout” or “washout” episodes, which often perplexes physicians [2]. The evaluation and determination of the exact cause of syncope is particularly challenging due to its multifactorial triggers [3]. Physicians and cardiologists often find it difficult to manage patients with recurrent, unexplained syncope as no diagnosis can be made possible in about 50% of cases [4].

Syncope due to orthostatic intolerance, is the second most common symptom, which is the key manifestation of autonomic failure [5–6]. Orthostatic hypotension (OH) is defined as a drop in systolic blood pressure (SBP) of ≥ 20 mm Hg or a drop in diastolic blood pressure (DBP) of ≥10 mmHg, within 3 minutes of standing, or head-up tilt (HUT) test to at least 60 degrees on a tilt table [6–7]. The tilt test measures the response of changes in heart rate and blood pressure in response to gravity. Disease-related causes of syncope range from common benign problems to severe life-threatening disorders [4]. To detect autonomic failure, tilt table testing has become a widely-accepted tool in the clinical assessment of patients presenting with syncopal manifestations. A passive tilt test provokes orthostatic stress, resulting in blood redistribution towards the lower parts of the body and circulatory adjustment by cardiovascular reflexes [8]. During orthostatic stress, the distribution of blood volume to maintain homeostasis is different between sexes [9].

Males and females differ in many aspects of physiology such as hormonal, haemodynamic, homeostatic balance, and many others. Very few studies have observed gender differences in orthostatic tolerance. One study observed a higher HR in females and higher DBP in males [10]. This finding contradicts another group of researchers, who did not find a gender difference in HR or mean arterial pressure (MAP) [11]. Due to these conflicting reports, our study was designed to investigate the gender effect on circulatory adjustment to postural challenge by tilt test.

Aim of the study

This study was aimed at measuring and comparing the changes in heart rate, systolic and diastolic pressure before and after tilt in both males and females.

Hypothesis

We hypothesized that there would be gender-related differences in the circulatory adjustment to a postural challenge.

Material and methods

Study design and setting

This study was carried out to observe the gender effect on cardiovascular response to tilt test in apparently healthy subjects of both sexes from March 2019 to February 2020 at the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka. Heart rate and BP changes after tilting were compared in healthy male and female subjects.

Study participants

A total of 90 apparently healthy male and female subjects between the ages of 18 and 60 years were recruited among the relatives and attendants of patients, hospital staff and students, through personal contacts and advertisement.

Measurement of blood haemoglobin, thyroid-stimulating hormone, serum alanine transaminase, serum creatinine, fasting blood sugar levels and electrocardiogram (ECG) was done to exclude subjects with diabetes, thyroid disorder, anaemia, liver disease, renal and cardiovascular disease. None of the participants had a history of fainting or unconsciousness or showed an abnormality on the ECG.

Study size and sampling

In this study, purposive sampling was done to select the participants. Our sample size was based on the estimation of differences in mean DBP between two groups (effect size) which was previously published in a similar study [12].

Ethical issues

The ethical and technical aspects of the study protocol involving human subjects was approved by the Institutional Review Board (IRB) of BSMMU.

Data collection

After informed written consent was obtained from the participants, they were requested to visit the Department of Physiology, BSMMU on a specified date. Detailed personal, medical, dietary, drug history and menstrual history was taken. Thorough physical examination was performed and height and weight were taken to calculate body mass index (BMI). All information was documented in a prefixed datasheet.

The tilt table test was performed in an autonomic nerve function laboratory in a quiet room, where ambient temperature was maintained at 25°C. The subjects were instructed to fast for at least one hour, asked not to drink or smoke, and asked to urinate. After 10 minutes of supine rest, tilting was done at a 60 degree angle using a motorized tilt table (Hi-Lo Mode; 220 volts; Cat No: IEMR4093HL; International Elecro Medical Co, India). Heart rate, systolic blood pressure and diastolic blood pressure were measured with a digital sphygmomanometer (Omron automatic blood pressure monitor: HEM-7120) and the mean arterial pressure (MAP) was calculated. Peripheral capillary oxygen saturation (SpO_2) was also measured by a fingertip pulse oximeter (YK-88LED). All aforementioned variables were recorded before and after tilting at 60 degrees, every minute for 10 minutes. To maximize the orthostatic stress, subjects were asked to avoid the movement of lower limbs.

Study outcomes

The primary outcome measures of this study included the maximum change in HR, SBP and DBP after tilting which is considered as the cardiovascular response to tilt test.

Statistical analysis

Data was expressed as mean ± standard deviation (SD) and percentage. Statistical analysis was performed using SPSS version 22. An independent samples t test was used to compare the confounding factors and study variables between males and females. Multiple regression analysis and chi squared tests were performed as applicable. A p value of <0.05 was considered to be statistically significant.

Results

Participants

A total of 100 subjects were examined for eligibility and 90 eligible subjects were enrolled. Data of all 90 subjects were included for analysis and there was no missing data.

General characteristics

In this study, there were no significant differences in mean age, BMI and the number of male and female participants. Blood pressure however, was significantly lower in females (Tab. 1).

Table 1. Age, BMI and blood pressure of males and females (n=90).

Variables	Male (n=45)	Female (n=45)	p value
Age (years)	40.05 ± 11.46	38.44 ± 10.57	0.493
BMI (kg/m2)	24.15 ± 3.15	24.65 ± 3.41	0.469
SBP (mm Hg)	121.42 ± 9.8	109.73 ± 13.1	0.001
DBP (mm Hg)	77.6 ± 7.8	70.55 ± 9.3	0.001

Data is expressed as mean ± SD. Statistical analyses were done by independent samples t test; n: number of subjects in each group.

Tilting

A lower drop in SBP, which was statistically significant, was found in females after tilting (Tab. 2).

Table 2. Drop in SBP, rise in DBP, rise in MAP, rise in HR and Drop in SpO_2 response in males and females (N=90).

Variables	Males (n=45)	Females (n=45)
Rise in HR (beats/min)	10.27 ± 6.44	10.51 ± 4.75
Drop in SpO_2 (%)	5.13 ± 4.36	5.05 ± 4.07
Drop in SBP (mm Hg)	6.82 ± 4.15	9.42 ± 5.31*
Rise in DBP (mm Hg)	8.38 ± 4.18	7.04 ± 4.66
Rise in MAP (mm Hg)	5.81 ± 3.77	5.26 ± 3.35

Data is expressed as mean ± SD. Statistical analyses were done by independent samples t test; HR: heart rate; SpO_2: peripheral capillary oxygen saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; number of the subjects in each groups; N: total number of subjects; *- p < 0.05.

A significant negative correlation of rise of HR ($p<0.05$) was found with older age and female subjects (gender). A significant positive correlation in drop of SBP ($p<0.05$) was noted with age, however a significant negative correlation was found with female subjects (gender) .In addition, there was a significant inverse relationship in the rise of DBP ($p<0.05$) and rise of MAP ($p<0.05$), which was noted with age only (Tab. 3).

In this study, a total of five (5.5%) subjects were affected with orthostatic intolerance. (Fig. 1). There were no significant differences in age and gender distribution of subjects with a positive outcome.

Discussion

In our study, the tilt response of all parameters was compared between females and males irrespective of age and BMI, to observe gender differences on the cardiovascular response to gravitational stress in apparently healthy subjects. A significantly greater drop in SBP was found in females compared to males. This finding is similar with that of Jarvis et al., who found a lower mean SBP and DBP in females but no difference in HR between females and males after tilt [10]. In contrast,

Table 3. Multiple regression analysis of rise in HR, drop in SBP, rise in DBP and rise in MAP (dependent variables) with age, BMI and gender (independent variables) (N= 90).

Variables		Coefficients		95% CI		p value
		B	β	Lower limit	Upper limit	
ΔHR	Constant	27.844		18.022	37.666	0.000***
	Age (years)	-0.164	-0.317	-0.265	-0.063	0.002**
	Gender	-0.443	-0.039	-2.664	1.778	0.014**
ΔSBP	Constant	2.244		-6.165	10.653	0.597
	Age (years)	0.140	0.312	0.053	0.226	0.002**
	Gender	-2.731	-0.279	-4.632	-0.829	0.005**
ΔDBP	Constant	8.426		0.788	16.06	0.031
	Age (years)	-0.163	-0.4	-0.242	-0.084	0.000***
	Gender	1.659	0.187	-0.068	3.386	0.06
ΔMAP	Constant	4.251		-2.207	10.71	0.194
	Age (years)	-0.082	-0.254	-0.149	-0.016	0.016**
	Gender	0.757	0.107	-0.703	2.218	0.222

Statistical analyses were done by multiple regression analysis; ΔHR: change in heart rate; ΔSBP: change in systolic blood pressure; ΔDBP: change in diastolic blood pressure; ΔMAP: change in mean arterial pressure; N: total number of subjects; ** - $p<0.01$; *** - $p<0.001$.

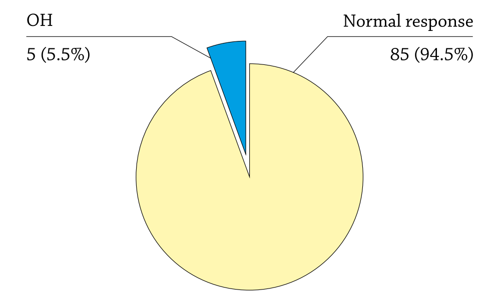

Figure 1. Frequency distribution (%) of all the study subjects with orthostatic hypotension (OH). Cut point of OH: drop in SBP ≥20 mm Hg and drop in DBP ≥10 mm Hg [7].

Schondorf and Low did not find any significant change in SBP between sexes following tilt test [11]. These authors suggested a gender-specific difference in BP regulation, and less orthostatic tolerance in females.

In the present study, no significant difference in post-tilt HR, SpO_2, DBP and MAP was found between females and males after tilting.

In addition, the comparison of orthostatic tolerance between females and males demonstrated a lower cardiovascular adjustment in females as evidenced by greater drop in SBP in response to postural challenge, suggesting a gender-specific difference in cardiovascular response to orthostatic stress. This is further supported by a higher frequency of OH in females. All these observations therefore suggest that females are more susceptible to orthostatic intolerance than males.

For further detail of variation of orthostatic tolerance due to phasic variation of menstrual cycle, previous studies suggested greater changes during the luteal phase [13–14]. Some studies, however, did not find any phasic difference in menstrual cycle in orthostatic tolerance [15].

In our study the phasic variation of the menstrual cycle on orthostatic stress on female was not explored.

In addition, the significant greater drop in SBP, observed in females than males strongly suggest less sympathetic response in females than males and the changes of baroreflex function maybe different between sexes [10–11].

This observed gender difference may be attributed to less splanchnic vasoconstriction and more blood pooling in the splanchnic region in females. This creates less venous return to the heart, less cardiac output and a greater drop in SBP in females [13].

The non-significant difference of DBP, MAP in the present study suggests that there was no difference in the compensatory increase of total peripheral resistance between females and males. A greater rise of DBP and MAP in males was associated with an increased peripheral resistance due to sympathetic over excitation [11].

Moreover, the non-significant difference of HR between females and males in this study suggests that there is no gender variation in parasympathetic response to postural change. Jarvis et al. also did not find HR differences between sexes [10]. Shoemaker et al. observed a significant increase in HR in females than that of males [16]. Conversely, HR was significantly higher in males than females which was witnessed by Schondorf and Low [11]. These investigators suggested that, the inhibitory baroreflex involved in the control of vasomotor and cardiomotor tone is less in females than males, which is responsible for less increment of HR in females [11]. Okada et al. also found lower baroreceptor sensitivity (BRS) in females than males [17].

In addition, difference of SpO_2 after tilt was not significant when compared between females and males in this study.

In our study, out of 90 apparently healthy subjects, 5 subjects developed OH. These subjects were greater in number, of older age, mostly females and overweight. All of the subjects were apparently healthy, and no one developed signs or symptoms of OH during tilt test. Four of them showed features of vasodepressor response (a drop in SBP ≥20 mm Hg and DBP ≥10 mm Hg) and one had psychogenic response (complaint of discomfort in absence of any remarkable change in haemodynamic response). None of them developed syncope.

Petersen et al. reported that 16 subjects developed OH out of 127 normal participants. Eleven of them had the features of cardioinhibitory response and five of them developed a vasodepressor response [18]. Very few subjects were accompanied by syncope.

It is noteworthy that from all this discussion, apparently healthy subjects may be at a risk of orthostatic intolerance in the absence of any underlying clinical disease. The evidence from the present study, and the findings of previous studies suggest that females are more prone to developing orthostatic intolerance in response to a tilt test [9].

Limitation of the study

This study could not assess the effect of cardiovascular responses to the tilt test in obese subjects. We also could not measure continuous beat- to- beat measurement of cardiovascular change during tilting. In addition, the effect of the menstrual cycle of females on cardiovascular response could not be evaluated.

Conclusions

Based on the results of the study, it can be concluded that females are more prone to orthostatic intolerance than males in response to tilting.

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Word count: 2271 • Tables: 3 • Figures: 1 • References: 18

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Rimi SA, Rezwana I, Sultana S, Ferdousi S.
Gender differences in circulatory adjustment to head-up tilt test in health.
MSP 2020; 14, 2: 10–14.

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Received: 7.04.2020
Reviewed: 25.05.2020
Accepted: 12.06.2020