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Influence of Gender on Cardiac Autonomic Reactivity in Young Adults

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Abstract
Our cardiovascular system is governed by autonomic nervous system. Since adults have lower cardiovascular risk, this study is aimed to find out gender differences in cardiac autonomic nervous activity by assessing various non-invasive tests like Lying to Standing test, Valsalva maneuver, sustained Hand grip test (HGT) and Cold pressor test (CPT). Study was done in healthy males and females ranging in age from 18 to 25 years. The mean basal systolic blood (SBP) pressure of males was significantly highly raised than females The mean SBP before and after HGT as well as CPT was higher for males than females and the difference was highly significant (P < 0.001). This study suggests, heart rate response to Standing and Heart rate changes during the Valsalva manoeuvre (Valsalva Ratio), denoting vagal activity, were not significantly different between males and females, whereas the SBP was more marked for males than females both before and after the stressors reflecting a higher sympathetic activity in males compared to females.
Keywords: *Autonomic nervous system, vagal activity, sympathetic activity, gender, hand grip test, cold pressure test.*

Introduction

The Autonomic Nervous System (ANS) establishes and maintains a dynamic adaptive state, permitting the organism to withstand innumerable perturbation to the ever-changing environment. ANS mediates changes in arterial blood pressure, heart rate and peripheral vascular tone to facilitate regional and systemic circulatory regulation.[1]Autonomic failure results in mild to severe degree of primary or secondary disorders such as hypertension, diabetes mellitus, alcoholism and amyloidosis etc depending on degree of dysfunction.[1]

The cardiovascular system under both physiological and pathophysiological condition is being regulated by ANS, thus [2] increasing attention is being focused on the normal functioning of ANS. Cardiovascular disease is recognized to show an increasing gender specific characteristic. There is a gender difference in terms of etiology, pathogenesis, clinical manifestations and outcomes of cardiovascular

diseases.[3] Various studies based on gender differences have revealed that men are generally at a greater risk for cardiovascular and renal disease than are age-matched, premenopausal women. National Health and Nutrition Evaluation Survey (NHANES III) showed that, in general, men had higher blood pressure than women through middle age. After menopause, however, blood pressure increases in women as well.[2] These differences in the incidence of cardiovascular diseases may be due to, gender difference in ANS, likely due to the developmental differences or due to the effect of prevailing levels of male and female sex hormones.[4,5]The cardiovascular responses of blood pressure, cardiac output, heart rate and other variables to change in posture differ between the sexes.[6] There are a few reports on gender-related differences in cardiac autonomic tone; also there are conflicting opinions about gender differences in ANS functions in males and females in younger age groups. The differences are related to greater decrease of thoracic blood volume with standing in women than the men. A few reports on gender-related differences in cardiac autonomic modulation reveal that, in normal population, parasympathetic tone dominates over sympathetic in women and vice versa in men.[7] Similarly, men were found to have higher plasma norepinephrine levels than women.[8] Yukishita et al. reported that in general autonomic activities attenuate with age in both genders.[9] However, the influence of gender on age-related changes in cardiac autonomic activity is not well established.

Over the past 10 years, differences between the physiology of men and women have been recognised with respect to the normal cardiovascular physiology as well as with respect to the incidence, severity and co-morbidities of obesity, diabetes and cardiovascular diseases. Physiologically the functional differences as well as the similarities are of utmost importance, as they provide fundamental insight into the mechanisms regulating the integrated functions of the intact organism.[4]

To our knowledge, only a few publications with rather conflicting results have focused on sex differences in cardiac autonomic function in healthy subjects. The data on this aspect was lacking in this part of the country, so the present study was conducted to measure the autonomic nervous system activity in adult males and females.

Material & Methods

A total of 150 healthy young adults (73 males and 77 females) were included in this study with age range from 18 to 25 years. The study was conducted in the Department of Physiology at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana (Ambala) from 2014 to 2015. The study was approved by institutional ethical committee. Informed and written consent of all the participants was taken before conducting the study. The non-smoker, non-alcoholic, non-diabetic, having normal pulse rate, with systolic and diastolic blood pressure < 140/90 mm/Hg and having no evidence of illness and having normal physical, mental and psychological well-being were included in the study. A brief history was taken and general physical examination of all the volunteers was done with main emphasis on cardiovascular diseases, renal diseases. None of the subjects took any medication at the time of study. All the students were explained about the procedure of tests and tested under similar laboratory conditions in comfortable environment. Detailed history was taken and clinical examination was done. Subjects were instructed not to have heavy meals/tea/coffee at least 2 hours before test and were asked to rest just before the commencement of test, and then all basal parameters like heart rate, blood pressure and respiratory rate were measured. Various Cardiovascular Autonomic function tests that were performed are as follows.

Tests of Cardiovascular Autonomic Function:

Parasympathetic tests:

1**.** Heart rate response to Standing.

2. Heart rate changes during the Valsalva manoeuvre.

Sympathetic tests

1. Blood pressure response to sustained Hand Grip Test.
2. Blood pressure response to Cold Pressor Test.

Heart rate response to Standing (Lying to Standing test)

In this test heart rate response to standing was assessed. Each subject initially took supine rest on a couch for 5 min; ECG limb leads were attached, base line ECG was recorded. Then subject attained standing posture within 3 seconds. A continuous ECG (lead II) was recorded during the procedure for measuring heart rate. 30:15 ratio was calculated as ratio of longest R-R interval at or around 30th beat after standing / shortest R-R interval at or around 15th beat after standing. Normal value of 30:15 ratio ≥ 1.04.[10]

Heart rate changes during the Valsalva manoeuvre (Valsalva Ratio)

The test was done in sitting posture. The subject blows into a mouth piece attached to sphygmomanometer to raise the pressure to 40 mmHg for 15 seconds. At the end of 15 seconds the pressure was released. A continuous ECG (lead II) was recorded 1 minute before the manoeuvre, during the manoeuvre and 40 seconds following release of strain period. Valsalva Ratio is calculated as ratio of longest R-R interval after the strain / shortest R-R interval during the strain. Normal value of Valsalva Ratio > 1.21.[10]

Blood pressure response to sustained Hand Grip Test (HGT)

The baseline blood pressure was recorded. The subject was asked to press handgrip dynamometer at 30% of maximum voluntary contraction (MVC) for 15 seconds. Blood pressure was recorded just before the release of hand grip after 1 minute and 5 min of grip release. Maximum rise in diastolic blood pressure above baseline was noted. A rise of more than 10 mmHg in diastolic blood pressure after test was considered normal.[11]

Blood pressure response to Cold Pressor Test (CPT)

First the baseline blood pressure was recorded then the subject was instructed about the test. He was instructed to indicate to the investigator if he was not able to keep the hand immersed in water for 1 minute. The cold water of 10^{o}C was prepared. Subject immersed the right hand in cold water up to the wrist without touching the bottom of cold water bath, for 1 minute. After that hand was removed from water, it was covered by the towel. The blood pressure was recorded from left hand just at the end of 1 minute of immersion and again at 1 minute after hand was withdrawn from the cold water. A rise of 10mmHg in diastolic blood pressure after test was considered normal.[10]

Each test was performed after a resting period of 10 minutes, in supine or sitting position. Blood Pressure recording was done by using an Omron (SEM 1 Model), the automatic blood pressure monitor (Omron Healthcare Co. Ltd, Kyoto, Japan). The heart rate was measured from R-R interval of ECG using lead II of Electrocardiograph machine (CADIART 108T-DIGI, BPL LIMITED). Hand grip strength was measured from Handgrip Dynamometer.

Statistical analyses

The collected data was tabulated and analyzed with the help of Statistical Package for Social Sciences SPSS for WINDOWSTM (version 20). Student's independent t test for quantitative differences was used for data analysis. Inter-group comparison was done by one way Anova with post hoc test. Mean ± standard deviations were calculated and t-test was applied for measuring statistical significance in difference of means. $P < 0.05$ was considered statistically significant and $P \leq 0.001$ was considered highly significant.

Results

In our study the total number of male subjects were 73 (48.70%) and females were 77 (51.30%). The mean age of males was 19.91±1.84 years and in females was 19.18±1.60 years which was

statistically not significant. Mean BMI among two groups was comparable, which was 23.8±2.33 kg/m² and 22.6±2.93 kg/m² for males and females respectively. Table 1 shows comparison of mean basal parameters (heart rate and blood pressure) between males and females. The mean basal heart rate of males was 79 ± 10.43 beats/min and females was 81.86 ± 9.39 beats/min which was not statistically significant (*P*= 0.08). The mean systolic blood pressure of males was (114.67 ± 9.14 mm/Hg) significantly highly raised than females (102.39 ± 7.65 mm/Hg) which was found statistically highly significant (*P* < 0.001). The mean diastolic blood pressure of males was 66.47 ± 8.54 mm/Hg and females was 64.14 ± 9.42 mm/Hg and the difference was not statistically significant (*P* = 0.12).

Table 2 shows the comparison of the two parasympathetic tests done i.e. Heart rate response to Standing (Lying to Standing test) and Heart rate changes during the Valsalva manoeuvre between males and females. There was no statistically significant difference in the mean value of 30:15 ratio between males and females (*P* = 0.354). In Valsalva manoeuvre, for males and females the mean of Valsalva ratio was 1.70 ± 0.28 and 1.71 ± 0.28 respectively (*P* = 0.806).There was no statistically significant difference in the values of both the parasympathetic tests in between males and females.

The comparison of the two sympathetic tests i.e. Blood pressure response to HGT and CPT between males and females are shown in Table 3. On comparison of two groups, mean SBP before and after HGT was found statistically very high for males than for females (*P* <0.001). But, the SBP difference of HGT for males and females was not statistically significant. The DBP difference of HGT for males as compared to females was also not significant.

In case of CPT, on comparison of mean SBP before and after CPT it was found that males had statistically high SBP before and after CPT than females (*P* < 0.001). But the SBP difference CPT for males (15.48 ± 7.93 mm/Hg) compared with females (16.68 ± 8.08 mm/Hg) was statistically insignificant (*P* = 0.362). Mean DBP before and after CPT for males and females, was also found to be statistically insignificant (*P* = 0.971). The mean DBP difference CPT was higher in males compared to females but it was not significant (*P* = 0.304).

Table 1 Comparison of Basal parameters between Males and Females

	Male (N=73) Mean ± SD	Female (N=77) Mean ± SD	*P* value*
Basal heart rate(beats/min)	79 ± 10.43	81.86 ± 9.39	0.08
Basal systolic pressure (mm/Hg)	114.67 ± 9.14	102.39 ± 7.65	**<0.001**
Basal diastolic pressure (mm/Hg)	66.47 ± 8.54	64.14 ± 9.42	0.12

*P-value <0.05 is considered statistically significant

Table 2 Comparison of Parasympathetic tests between Males and Females

	Male (N=73) Mean ± SD	Female (N=77) Mean ± SD	*P* value*
LYING TO STANDING TEST			
R-R interval at 30th beat	16.66 ± 2.52	16.35 ± 2.76	0.477
R-R interval at 15th beat	13.03 ± 1.99	13.01 ± 2.04	0.965
30:15 ratio	1.30 ± 0.15	1.27 ± 0.15	0.354
VALSALVA MANOEUVRE			
longest R-R interval after the strain	21.53 ± 3.28	20.80 ± 3.25	0.173
shortest R-R interval during the strain	12.82 ± 2.21	12.40 ± 1.80	0.200
Valsalva Ratio	1.70 ± 0.28	1.71 ± 0.28	0.806

*P-value <0.05 is considered statistically significant

Table 3 Comparison of Sympathetic tests between Males and Females

Blood pressure (mm/Hg)	Male N=73 Mean ± SD	Female N=77 Mean ± SD	*P* value*
HAND GRIP TEST (HGT)			
SBP Before HGT	117.67 ± 9.18	104.70 ± 8.78	**<0.001**
SBP After HGT	138.60 ± 12.83	125.42 ± 14.85	**<0.001**
SBP Difference HGT	21.45 ± 9.82	21.18 ± 11.28	0.876
DBP Before HGT	68.58 ± 9.05	67.64 ± 6.75	0.475
DBP After HGT	85.26 ± 12.10	85.71 ± 11.13	0.812
DBP Difference HGT	17.52 ± 8.46	17.99 ± 8.60	0.738
COLD PRESSOR TEST(CPT)			
SBP Before CPT	116.68 ± 9.46	104.92 ± 8.42	**<0.001**
SBP After CPT	132.21 ± 11.65	121.47 ± 11.99	**<0.001**
SBP Difference CPT	15.48 ± 7.93	16.68 ± 8.08	0.362
DBP Before CPT	67.81 ± 8.03	66.88 ± 6.83	0.450
DBP After CPT	82.82 ± 9.87	82.88 ± 10.50	0.971
DBP Difference CPT	15.05 ± 5.52	16.05 ± 6.31	0.304

*P-value <0.05 is considered statistically significant

Discussion

The present study examined the effect of gender on cardiac autonomic activity. Evaluation of status of autonomic nervous system was assessed with the help of various non-invasive tests like Lying to Standing test, Valsalva maneuver, sustained Hand grip test and Cold pressor test. Evaluation of parasympathetic system tests primarily provide an index to cardiac vagal functions. While, symapathetic tests are of prognostic importance to determine sympathetic reactivity. The findings of our study indicated that mean basal SBP (Table 1) of males was significantly raised than females (P < 0.001). While the mean basal diastolic blood pressure of males (66.47 ± 8.54 mm/Hg) was also higher than females (64.14 ± 9.42 mm/Hg) but the difference was not statistically significant. Wiinber at el. studied normotensive men and women and found men had higher 24-hour mean blood pressure, by approximately 6 to 10 mm Hg, than did women. Similarly Khoury at el. performed ambulatory blood pressure monitoring on men and women and found that men had higher blood pressure than did women.[12]

Comparison (Table 1) of mean basal heart rate for females (81.86 ± 9.39 beats /min) was found to be higher than in males (79 ± 10.43 beats /min) but the difference was not found to be statistically significant(P = 0.08). A lower mean basal heart rate in males is unexplained, but may derive from different neurohumoral and central autonomic mechanisms in males and females rather than solely from differences in autonomic outflow. The higher basal heart rate in females can also be related to a lower stroke volume.

The 30:15 ratio and Valsalva ratio (Table 2), denoting vagal activity, were not significantly different between males and females. The mean SBP before and after HGT as well as CPT (Table 3) was higher for males than females and the difference was highly significant (P < 0.001). Our findings indicate that systolic blood pressure was more marked for males than females both before and after the stressors. Interpretation of the results of human responses to stressors requires consideration that women apparently perceive the relative strength of stressors differently to men.[13] Light KC et al. and Stoney et al. have reported that males show a greater response in systolic blood pressure to a number of cardiovascular stressors.[14,15] Some but not all studies have however found gender differences in the response to parasympathetic tests (valsalva and deep breathing).[16] Various studies using heart rate variability as an indicator to access autonomic functions, have observed a higher HFnu and HF/LF ratio in the female subjects which can be attributed to lower sympathetic activity in females which is reflected by lower LF in absolute and relative values in females.[17,18] Higher LF power in

men has been found in several studies . These data suggest that males have a preponderance of sympathetic over vagal control of cardiac function compared with females.[18]

Ramaekers et al., in his study postulated that lower sympathetic activity in females compared to males might provide an explanation for the protection against cardiovascular disease observed in females.[19] Various other studies have also observed that females display lower sympathetic activity and increased cardiac vagal modulation which could reflect the lower incidence of arrhythmias, high blood pressure and sudden cardiac death compared to males.[20,21,22,23,24,25]

Gender differences in the autonomic nervous system may be present because of developmental differences or due to the effects of prevailing levels of male and/ or female sex hormones.[2] A few studies have indicated that female sex hormones influence autonomic modulation and estrogen has a facilitating effect on cardiac vagal function.[26] In addition, ovarian hormones have also been shown to influence autonomic cardiovascular regulation[23] by preventing sympathovagal imbalance and improving [24] baroreflex sensitivity.[25] Estrogen improves vasomotor tone and vascular integrity, lowers blood pressure, and improves lipid profiles and cholesterol metabolism.

Estrogen has been shown to stimulate nitric oxide (NO) production. Evidence suggests that NO plays a major role in regulating blood pressure, as NO diffuses across the endothelium into neighbouring smooth muscle and induces vasodilation.[27,28] On the other hand, increases in androgens in humans and animal studies have shown to increase blood pressure.[12] The mechanisms underlying the paradoxal gender difference in cardiac autonomic function are obscure. It remains to be proven, however, that the difference in behaviour of the cardiac autonomic nervous system in males and females substantially contributes to the large gender differential in morbidity and mortality of heart disease, which cannot be explained by the presently known standard risk factors.[29]

In summary, heart rate response to Standing and Heart rate changes during the Valsalva manoeuvre (Valsalva Ratio), denoting vagal activity, were not significantly different between males and females, whereas the SBP was more marked for males than females both before and after the stressors reflecting a higher sympathetic activity in men compared to women.

Limitations of the study

The sample size in the present study is moderate, especially the sample was drawn from one limited geographical area, which is inadequate for extrapolating the application of these findings to the general population. Also, we have not estimated male and female sex hormones to correlate the influence of gonadal hormones on autonomic reactivity and CV risks in both the genders. Therefore, future studies with larger sample size are warranted for detailed of assessment of gender on autonomic functions in different age groups

Bibliography

1. Rosenwinkel ET, Bloomfield DM, Arwady MA, Goldsmith RL. Exercise and autonomic function in health and cardiovascular disease. Cardiology Clinics. 2001; 19(3):369-87.
2. Xiao-Ju D and Kingwell BA. Gender, sex hormones and autonomic nervous control of cardiovascular system. Oxford Journal. 2002; 53(3): 678-87.
3. R Gupta, P Joshi, V Mohan, K S Reddy, S Yusuf. Epidemiology and causation of coronary heart disease and stroke in India. Heart. 2008;94:16-26.
4. Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. Adv Physiol Educ 2007; 31(1):17-22.

5. Jane F. Reckelhoff. Gender Differences in the Regulation of Blood Pressure. Hypertension. 2001;37:1199-1208
6. Moodithaya S, Avadhany S. Gender differences in age-related changes in cardiac autonomic nervous function. J Aging Res. 2012;2012:679345.
7. Kuo TBJ, Lin T, Yang CCH, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. American Journal of Physiology. 1999;277 (6):2233-9.
8. Geelen G, Laitinen T, Hartikainen J, et al. Gender influence on vasoactive hormones at rest and during a 70 degree head-up tilt in healthy humans. J Appl Physiol. 2002;92(4):1401-8.
9. T. Yukishita, K. Lee, S. Kimet al. Age and sex dependent altertations in heart rate variability; profiling the characteristics of men and women in their 30. Journal of Anti-Aging Medicine. 2010;7(8): 94–9.
10. Khandelwal E, Jaryal AK, Deepak KK. Cardiovascular autonomic functions & cerebral auto regulation in patients with orthostatic hypotension. Indian J Med Res. 2011; 134(4): 463-9.
11. Deepak D, Sinha AN, Gusain VS, Goel A. A study on effect of meditation on sympathetic nervous system functional status in meditators. Journal of Clinical & Diagnostic Research. 2012; 6(6): 938-42.
12. Reckelhoff JF. Gender differences in the regulation of blood pressure. Hypertension. 2001;37:1199-208.
13. Lash SJ, Gillespie BL, Eisler RM, Southard DR. Sex differences in cardiovascular reactivity: effects of the gender relevance of the stressor. Health Psychol 1991;10:392–98.
14. Stoney CM, Davis MC, Matthews KA. Sex differences in physiologyical responses to stress and in coronary heart disease: a causal link. Psychophysiology. 1987; 24: 127–31.
15. Light KC, Turner JR, Hinderliter AL, Sherwood A. Race and gender comparisons, Hemodynamic responses to a series of stressors. Health Psychol. 1993; 12: 354–65
16. Schondorf R, Low PA. Gender related differences in the cardiovascular responses to upright tilt in normal subjects. Clin Auton Res. 1992; 2: 183–87.
17. Madden K, Savard GK. Effects of mental state on heart rate and blood pressure variability in men and women. Clin Physiol 1995; 15:557–69.
18. Yamasaki Y, Kodama M, Matsuhisa M et al. Diurnal heart rate variability in healthy subjects: effects of aging and sex difference. Am J Physiol 1996;271:303–10.
19. D. Ramaekers, H. Ector, A. E. Aubert, A. Rubens, F. Van De Werf. Heart rate variability and heart rate in healthy volunteers: is the female autonomic nervous system cardioprotective?. European Heart Journal, 1998.19;(9):1334-41
20. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. J Cardiovasc Electrophysiol. 1998;9(6):655-64.
21. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Asso-ciation Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113(6):85-151.
22. Benjamin IJ, Christians E. Exercise, estrogen, and ischemic cardioprotection by heat shock protein 70. Circ Res. 2002;90 (8):833-5.
23. Minson CT, Halliwill JR, Young TM, Joyner MJ. Influence of the menstrual cycle on sympathetic activity, baroreflex sensitivity, and vascular transduction in young women. Circulation. 2000;101 (8):862-8.

24. Saleh TM, Connell BJ. Estrogen-induced autonomic effects are mediated by NMDA and GABAA receptors in the parabrachial nucleus. Brain Res. 2003; 973(2):161–70.
25. Mohamed MK, El-Mas MM, Abdel-Rahman AA. Estrogen enhancement of baroreflex sensitivity is centrally mediated. Am J Physiol. 1999;276(4):1030-7.
26. X. J.Du, A. M. Dart, and R. A. Riemersma. Sex differences in the parasympathetic nerve control of rat heart. Clinical and Experimental Pharmacology and Physiology. 1994;21(6):485-493.
27. Hermann M, Flammer A, Luscher TF. Nitric oxide in hypertension. J Clin Hypertens. 2006;8(12):17-29.
28. Klahr S. The role of nitric oxide in hypertension and renal disease progression. Nephrol Dial Transplant. 2001;16(1):60-2.
29. Eaker ED, Packard B, Thom TJ. Epidemiology and risk factors for coronary heart disease in women. Cardiovasc Clin. 1989;19:129-45.