Gender Differences in Response to Cold Pressor Test in the Age Group of 18-30 Years

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Abstract

Introduction: The Cold Pressor Test (CPT) was first introduced by Hines and Brown in 1932. It was designed to measure the reactivity of the blood vessels to a standard stimulus[2]. Cold Pressor Test is an established challenge test of sympathetic vascular regulation. Sympathetic nervous system activity varies in males and females.

Aim: To study the response of Cold Pressor Test on blood pressure in normal healthy young adult males and females.

Materials and Method: After Institutional ethics committee approval, a total of 104 subjects in the age group of 18-30 years were recruited with informed consent for the study, after considering inclusion and exclusion criteria. Subjects were explained about the test procedure. Basal blood pressure (pre-test BP) was recorded after 20 min. of rest. Systolic and diastolic blood pressure was measured in mmHg (pre-test). Subject was asked to dip left hand till the wrist in cold water (4^0-8^0 C) for 1 min. (minute).Blood pressure was recorded from right arm during the test, 1 minute, 2 minutes, 3 minutes and 4 minutes after the test.

Result: Basal BP was significantly higher in males than in females. Systolic BP(SBP) response, Diastolic BP response (DBP) to CPT were statistically higher in males compared to females.

Conclusions: The gender variations are seen due to differences in the sympathetic nervous system activity and due to the effect of sex hormones. Males are more prone to develop hypertension and other cardiovascular disorders when compared to females due to higher sympathetic activity.

Keywords: *Cold Pressor test, sympathetic nervous system, males, females.*

Introduction

The subjects prone to develop hypertension in later life have a period of underlying sympathetic overactivity[1]. Increased sympathetic and decreased parasympathetic activities in young adults alters sympathovagal balance, which could be the major mechanism in causation of pre hypertension[3]. Sustained sympathetic overactivity has been reported as among the primary mechanisms for genesis of essential hypertension[2]. The subjects at risk of developing hypertension can be identified by performing the CPT.

The Cold Pressor Test (CPT) was first introduced by Hines and Brown in 1932. It was designed to measure the reactivity of the blood vessels to a standard stimulus[2]. (CPT) is an established challenge test of autonomic vascular regulation. This study aims to study the gender variation in response to CPT, giving insight into level of sympathetic activity, and subsequent risk of developing hypertension in future and other cardiovascular disorders.

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Materials and Method

104 Subjects 18-30 years, studying in Osmania Medical College.

Inclusion Criteria:

Healthy Young adult offspring of

1. Normotensive parents.
2. Either one or both parents can be hypertensive.

Exclusion Criteria:

Subject with history of

1. Hypertension
2. Diabetes Mellitus
3. Cardiovascular disorders
4. Neuropathy
5. Addictions to tobacco/alcohol.

Materials and Method

Mercury Sphygmomanometer, Stethoscope, Thermometer, Timer, Ice water at 4°-8°C, Stadiometer, Weighing machine.

Instructions:

Subjects were asked

1. Not to have caffeine rich drinksat least 2-3 hour prior to test.
2. Not to perform Valsalva manoeuvre & isometric contraction during the test.

Procedure: After Institutional ethics committee approval, with informed consent subjects were recruited for the study. Details regarding the health status, past medical history, past cardiac surgeries, family history of hypertension (in parents), addictions were obtained. Subjects were explained about the test procedure. Basal blood pressure (pre-test BP) was recorded after 20 minutes of rest. SBP & DBP was measured in mmHg (pre-test). Subject was asked to dip left hand till the wrist in cold water (4°-8°C) for 1 minute. Blood pressure was recorded from right arm during test, 1 minute, 2 minute, 3 minute & 4 minute after the test.

Statistical analysis: Unpaired t test was used to find the significance between various parameters. p value <0.05 was considered as statistically significant (*).

Observation and Results:

Table 1: Characteristics of male and female subjects

Parameter	Male	Female	p value
Number	45	59	-
Age (years)	19.78±2.89	20.50±3.97	0.294
Height (meters)	1.671±0.71	1.58±0.091	0.001*
Weight (kg)	59.89±10.71	56.93±11.54	0.185
BMI (kg/m^2)	24.06±4.67	25.90±4.20	0.037

Table 2: Comparison of Basal Blood Pressure (mmHg) between males and females

Parameter	Male	Female	p value
Basal SBP	110±8.52	101.70±9.86	0.001*
Basal DBP	72.67±5.94	69.29±7.22	0.01*

Table 3: Comparison of Systolic Blood Pressure response to CPT (mmHg) between males and females

Parameter	Male	Female	p value
Basal SBP	110±8.52	101.70±9.86	0.001*
During test	127.42±9.48	119.12±10.76	0.001*
1min after test	115.91±11.26	107.56±11.79	0.001*

Parameter	Male	Female	p value
2min after test	109.20±9.12	102.10±10.35	0.001*
3 min after test	108.09±8.92	100.91±9.53	0.001*
4 min after test	107.46±9.18	99.93±9.07	0.001*
Maximum SBP	127.42±9.48	119.12±10.76	0.001*
Change in SBP	16.18±7.45	16.91±8.19	0.637

Table 4: Comparison between Diastolic Blood Pressure (mmHg) response to CPT between males and females

Parameter	Male	Female	p value
Basal DBP	72.67±5.94	69.29±7.22	0.01*
During test	86.98±10.50	69.29±7.22	0.01*
1min after test	77.87±8.81	72.10±9.67	0.002*
2min after test	73.91±6.22	69.53±8.41	0.005*
3 min after test	73.02±6.61	68.47±7.61	0.002*
4 min after test	72.89±6.61	68.03±7.40	0.001*
Maximum DBP	86.76±10.76	81.22±9.04	0.005*
Change in DBP	13.73±8.47	11.18±6.50	0.086

Discussion

Males had higher basal SBP (110±8.52mmHg) & higher DBP (72.67±5.94mmHg) compared to basal SBP (101.70±9.86mmHg) & basal DBP (69.29±7.22mmHg) in females, which was statistically significant (p=0.001). This is in accordance with study done by Weiinber & colleagues[4], Khoury et al[5], a meta- analysis study by Staessen et al[6], The third National Health & Nutrition Evaluation Survey[7] (NHANESIII).

BP recordings during CPT & sequentially every minute thereafter up to 4 minutes, reveal statistically significant higher values in males compared to females. The higher SBP in males (127.42± 9.48mmHg) during CPT when compared to females(119.12±10.76mmHg) correlating with Srivastava et al[8] (P=0.001).

BP measurement continued after the removal of hand from the cold water in order to detect delayed pressor effect and duration of elevated blood pressure.

The SBP values 1 minute after the test were higher in males (115.91±11.26mmHg) than in females (107.56±11.79mmHg). The SBP values 2 minutes, 3 minutes, 4 minutes after test were significantly higher in males than in females.

The maximum SBP attained in males was higher (127.42±9.48 mmHg) than in females (119.12±10.76mmHg) & the p value was statistically significant (p=0.001). The change in SBP (Maximum SBP minus Basal SBP) was higher in females (16.91±8.19mmHg) than in males (16.18±7.45mmHg) and was not statistically significant (p=0.637). The change in SBP was higher in females correlating with Srivastava et al[8].

The DBP response to CPT during test was higher in males (86.98±10.50mmHg) than in females (69.29±7.22 mmHg) & the values were statistically significant (p=0.001) correlating with Srivastava et al[8]. Males had higher DBP values 1 minute, 2 minutes, 3 minutes & 4 minutes after the test than females. Maximum DBP attained was higher in males than in females. The change in DBP was more in males (13.73±8.47mmHg) than in females (11.18±6.50 mmHg) in contradiction to Srivastava et al.[8] with a higher change in DBP in females than in males.

Mechanism of CPT induced increase in BP[9]: When the hand is immersed in cold water (4°-8°C), the A & C fibres are activated in response to pain, temperature sensation. These fibres ascend contralaterally as

anterolateral system which includes Spinothalamic, Spino-reticular & Spino-mesencephalic tracts. The nociceptive specific neurons ascend in the lateral mesencephalon, while the thermoreceptive specific neurons project to Dorsomedial part of ventro posteromedial nucleus of Thalamus. The ascending fibres of spinoreticular tract project to medullary reticular formation, via the Ionotropic Glutamate receptors activate the Rostral Ventrolateral Medullary (RVLM) neurons resulting in increased sympathetic nervous activity leading to increase in blood pressure, heart rate, total vascular resistance, muscle sympathetic activity[10,11,12], decrease inforearm blood flow[13]. Thus, CPT increases the sympathetic nervous system activity to increase the BP which depends on the sympathetic tone.

In the present study, males had higher:

1. Basal SBP & DBP
2. SBP & DBP during the test
3. SBP & DBP 1 minute, 2 minutes, 3 minutes & 4 minutes after the test.

Gender variations to CPT is due to androgens, estrogen, progesterone.

Androgensplays a crucial role in gender differences in blood pressure regulation. The probable mechanisms by which androgens lead to increased blood pressure are: Androgens lead to increased formation of Angiotensin II, which increasesoxidative stress leading to production of superoxide, quenching of Nitric Oxide, and also reducethe renal vascular response to vasodilators, including residual Nitric Oxide(NO). Androgens also cause production of F2-isoprostanes which potentiate the effect of Ang II as avasoconstrictor, and alsostimulate endothelin-1 production to increase blood pressure further.[14]

Estrogens and their receptors play a crucial role in endothelium-dependent maintenance of vascular tone[15-17]. Estrogenscause relaxation via endotheliumderived hyperpolarizing factor (EDHF), by inducing vasodilator prostanoids (PGE2, PGI2), and by inhibiting endothelin-1 production[18]. Endothelial progenitor cells (EPCs) also play a crucial role in vascular response. Fertile females havehigher levels of EPC than men. Intrinsic differences within the endothelial cells contribute to differences between men and women. Other factors that modulate autonomic cardiac activity, may influence sex differences, such as inflammation, increased pain sensitivity to cold, and psychological disorders (e.g. depression). Healthy females have a lower central sympathetic neural output to periphery and a lower sympathetic vasoconstrictor drive when compared to healthy men.[19] Studies done at molecular level indicate that centralactions of estrogens include facilitation of cholinergic transmission and activating the synthesis of a vital rate limiting enzyme choline acetyltransferase, involved in the formation of acetylcholine formation, and also have a role in sympathetic outflow inhibititon[20,21]

Estrogen[22] decreases the production of cyclo-oxygenase derived products, reactive oxygen species, angiotensin-II & endothelin-1 which are vasoconstrictor agents. It inhibits smooth muscle cells by activating K+ efflux & by inhibiting calcium influx through inhibition of L-type Ca^{2+} channels and decreases myosin light chain phosphorylation and contraction of smooth muscle. Estrogen also inhibits proliferation of vascular smooth muscle cell.

Membrane-impermeant forms of estrogenacts oncell surface estrogen receptors, leading to the activation of mitogen-activated protein kinase (MAPK) and increased cGMP production and nitric oxide (NO) release.

Estrogenacts on the renin-angiotensin system is at the formation of Ang II, at the Ang II receptors level and on Ang II-induced responses[22]. Estrogen increases gene expression and plasma levels of angiotensinogen and antagonizes the AT1 receptor-mediated growth-promoting effects of Ang II in vascular smooth muscle cells. Estrogenacts on the endothelin-1 (ET-1) pathway at different levels: at its formation, at level of the receptors and on ET-1-induced responses.

The luteal phase is associated with a significantly reduced parasympathetic activity. The high progesterone levels during the luteal phase may have an inhibitory role on cardio-vagal activity[22-25]. Studies showed a higher sympathetic activity and a sympathovagal imbalance in luteal phase with an associated increase in parasympathetic activity in follicular phase,showing sympathetic predominancein luteal phase [26-29]. In physiological doses, progesterone acts as a sympathomimetic agent which induces nor epinephrine release[30,31]

The results corroborates with report by Weitz et al[32], that the activity of sympathetic nervous system shows

gender specific differences with lower sympathetic nerve activity to muscle vascular bed in women as compared with men, the difference vanishes after menopause.

Thus, the female sex hormones together cause lower BP response to CPT in females.

Conclusion

Males had significantly higher values for - Basal SBP & DBP, SBP & DBP values during the test, SBP & DBP values 1 minute, 2 minutes, 3 minutes & 4 minutes after test, Maximum SBP & Maximum DBP than females.

The gender variations are seen due to differences in the sympathetic nervous system activity and due to the effect of sex hormones. Males are more prone to develop hypertension and other cardiovascular disorders when compared to females due to higher sympathetic activity.

The Change in SBP & change in DBP values between males and females are not statistically significant.

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