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## Evaluation of Autonomic Responses in Male Patients suffering with Chronic Pain using Valsalva Maneuver and Tilt Table Test.

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### ABSTRACT

Chronic pain is the most common cause of the disablement in the world. This study was conducted to understand the effects of chronic pain on autonomic responses by using Valsalva maneuver (VM) and Tilt Table Test (TTT). Fifty male patients having the pain of musculoskeletal origin with chronicity of > 6 months duration and severity of > 3 on visual analogue score were included in the study. The same numbers of age-sex matched controls were also selected. The blood pressure and ECG was recorded during VM and TTT. The Valsalva ratio and 30 : 15 ratio was calculated. During VM, there is significant decrease in the Valsalva ratio in the cases ( $P < 0.05$ ). During TTT, there is significant decrease in 30 : 15 ratio and significant increase in SBP in the cases ( $P < 0.05$ ). In conclusion, the Valsalva ratio in the cases are decreased indicating the decreased parasympathetic / increased sympathetic reactivity which is further supported by the decrease in 30 : 15 ratio observed during Tilt Table Test. The increase in SBP in cases also supports the shifting of sympathovagal balance towards the sympathetic side.

**Keywords:** Valsalva Maneuver, Tilt Table Test, Pain, Sympathetic and Parasympathetic Reactivity.

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## INTRODUCTION

It is well known that autonomic nervous system regulates the visceral functions like heart rate, intestinal motility, urination, sexual activity and many other functions. As the human body tries to adjust according to the changes in the external and internal environment, it is constantly being exposed to various forms of stresses. Many ongoing researches have shown correlation between chronic pain and blood pressure alteration, which is mediated by baroreceptors, endogenous opioid activity and noradrenergic system [1] thereby involving both sympathetic and parasympathetic systems. Various works have been conducted on autonomic functions in chronic pain patients but they are not able to prove the dominance of sympathetic system or parasympathetic system in producing the responses [2-3].

Prolonged pain of musculoskeletal origin causes alterations in the sympathetic and parasympathetic outflow. Sympathetic hyperactivation has already been shown in fibromyalgia [4], migraine [5], chronic neck and shoulder pain [6]. The sympathetic and parasympathetic systems work together to maintain harmony of the human physiological system but this state can be disrupted by the chronic pain. The autonomic nervous system governs the cardiovascular system and this fact has resulted to various studies showing relations between autonomic dysfunction and chronic pain [2-3]. Since any alterations in the autonomic nervous system bring about the changes in the cardiovascular parameters like blood pressure (BP) and heart rate (HR) therefore, Valsalva maneuver (VM) and Tilt Table Test (TTT) were performed in this study to evaluate the autonomic reactivity. Individual characteristics that influence changes in heart rate during the Valsalva maneuver include age, systolic blood pressure (SBP) and physical activity [7-10]. It is also reported that the Valsalva ratio did not depend on the individuals resting heart rate [10].

Though studies on the effect of chronic pain on autonomic reactivity have been carried out by some other workers elsewhere [2-3] but the same study has not been conducted yet in the population of Eastern Uttar Pradesh, India to the best of our knowledge. Therefore, this study was planned to evaluate the autonomic responses in the male patients suffering with chronic pain and the age-sex matched controls of Eastern Uttar Pradesh, India.

## MATERIALS AND METHODS

After getting approval from Ethical Committee, Institute of Medical Sciences, Banaras Hindu University, Varanasi; present study was conducted to understand the autonomic reactivity in the chronic pain patients and age-sex matched controls by using Valsalva maneuver and Tilt Table Test. All the patients were informed about the study and were enlisted after their written consent.

### Selection of Cases and Controls

Those patients suffering with chronic pain of musculoskeletal origin of severity > 3 on visual analogue score (VAS) and of duration > 6 month were included in this study. The history of diseases like hypertension, diabetes mellitus, hyper/hypothyroidism, uremia etc or the use of any medication like diuretics, calcium channel blocker, neuroleptics, antiepileptic, antidepressant and  $\alpha / \beta$  blockers was considered as exclusion criteria in the selection of patients. The age and sex matched healthy persons were selected for the comparisons of various parameters and were defined as control. Fifty male cases were selected from the Pain Clinic, Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, based on the exclusion and inclusion criteria as mentioned above in this paragraph. Non-random method was adopted for the selection of the cases during the period of 1 year. Fifty age-sex matched controls were also selected in this study for the comparisons of the various parameters.

### Study design

The patients were advised to avoid the foods and drinks which contain caffeine and nicotine at least 12 hours prior to the recording. They were also told to avoid the strenuous activities such as running and jumping at least two hours prior to the recordings. Patients were advised to take light meal containing less fat and no alcohol with 6-8 hours of deep sleep in the previous night. All tests were performed between 9 AM to 12 Noon after a light breakfast. The temperature of the laboratory was maintained at  $25 \pm 2$  °C, with minimum light and noise. The patients were briefed about the various procedures. The patients were allowed to lie

down on the bed and were given 10-15 minutes of rest before the onset of recordings. The BP was measured by using digital blood pressure apparatus (Omron Health Care co. limited, Japan) and electrocardiogram (ECG) and respiration (by using stethograph) were recorded by POLYRITE-D (RMS, Chandigarh, India). Further, heart rate (HR), Valsalva ratio and 30:15 ratio was computed from the E.C.G.

### **Valsalva Maneuver (VM)**

The VM comprises an abrupt transient voluntary elevation of intrathoracic and intra-abdominal pressures provoked straining. For this purpose, the patient blows into the mouth piece of an aneroid manometer up to 40 mm Hg for 15 seconds. Interpretation of the test is more accurately performed by Valsalva ratio; it is the ratio of longest R-R interval within 20 beats of ending manoeuvre to shortest interval during manoeuvre. In this study, a plastic disposable mouthpiece was placed in the tube of aneroid sphygmomanometer with patient in sitting position and ECG leads were connected in standard limb lead- II configuration. The patient breathes into disposable plastic mouthpiece attached to aneroid manometer to maintain pressure at 40 mmHg for 15 s. ECG was recorded up to 45 s after the manoeuvre and the Valsalva ratio was computed manually. This was repeated twice more and the average of the ratio from the 3 Valsalva attempts was considered as the final result. Valsalva ratio  $>1.21$  is considered as normal and  $< 1.21$  as abnormal value.

### **Tilt Table Test (TTT)**

Blood pressure, heart rate and respiratory changes were recorded initially in resting condition while patients were lying on the Tilt Table horizontally. The Tilt Table is self designed, manually driven and made by a local carpenter which enables the table  $90^{\circ}$  vertical within 3-4 s. This is the advantage of our Tilt Table over the electric motor driven Tilt Table which takes 10-15 s time in changing the posture which may allow the person for adjustment of the cardiovascular parameters.

In TTT, the HR changes and SBP changes occurring due to the postural changes were observed. The posture was changed from lying to standing expecting for maximum orthostatic effects on cardiovascular system. 30 : 15 Ratio was calculated after the tilting of table at  $90^{\circ}$  for the assessment of HR functions. Difference in SBP between lying and after standing for 1 minute was recorded and the values were interpreted. Any decrease in SBP  $< 10$  mmHg was considered as normal, between 11-20 mm Hg as borderline and  $> 30$  mm Hg as abnormal value.

### **Statistical Analysis**

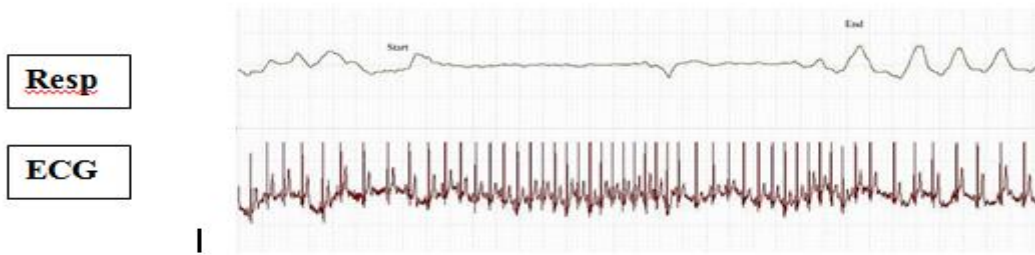
Data is presented in the form of mean and SEM. Statistical analysis is done by using Graph Pad Prism version-6. Unpaired student's t-test was used wherever required. A  $p$  value  $< 0.05$  is considered as significantly different.

## **RESULTS**

### **Valsalva Maneuver**

The international normative longest to shortest ratio of R-R interval (Valsalva ratio) during Valsalva maneuver is  $\geq 1.21$  and considered abnormal, if it's less than  $\leq 1.21$ . In our study the mean Valsalva ratio of male cases is  $1.03 \pm 0.03$  and mean Valsalva ratio in male controls is  $1.28 \pm 0.04$ . When compared, it was found significantly lesser than each other ( $p < 0.05$ ; Fig 1 and 2).

**Male case**



**Male control**

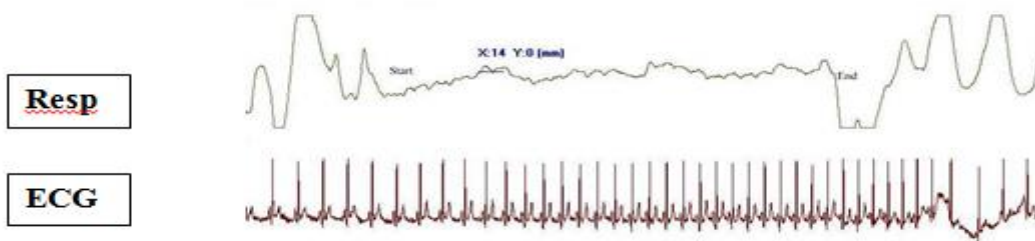


Figure-1 Original tracings showing Valsalva maneuvers in male cases and male controls. Speed = 15 mm/s, Sensitivity = 500  $\mu$ v for respiration and 50  $\mu$ v for ECG.

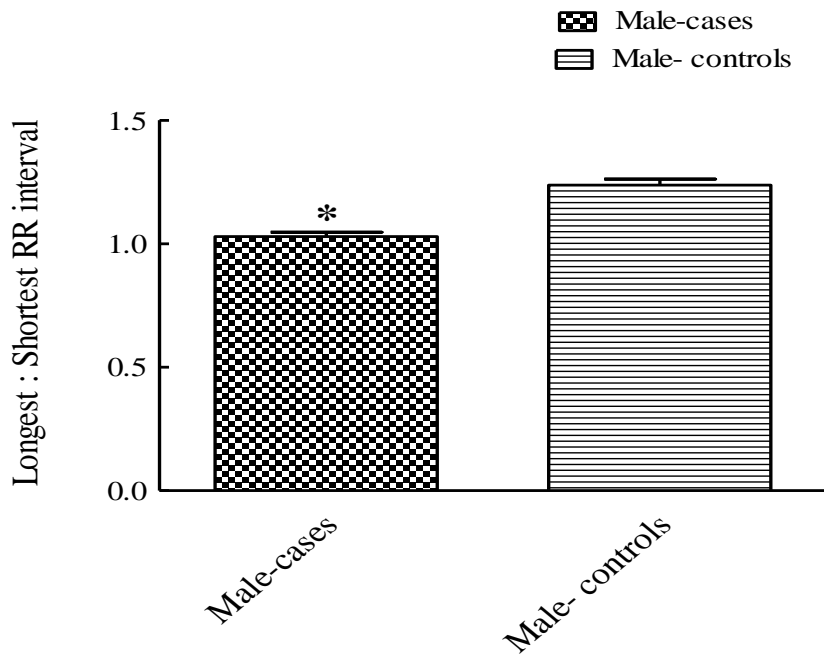


Figure-2 The histogram showing Longest : Shortest RR interval (Valsalva ratio) during Valsalva maneuver in male cases and male controls. Data represents the mean  $\pm$  SEM value of male cases and male controls. An asterisk “\*” indicates  $p < 0.05$  as compared to the controls.

When the Valsalva ratio of male controls (1.28  $\pm$  0.04) was compared with the Valsalva ratio of international normative values ( $\geq 1.21$ ), it was found greater but not significantly different than the later.

**Tilt Table Test (lying to standing)**

**HR changes (30:15 ratios)**

The normative international HR response (R-R interval ratio at 30<sup>th</sup> beat : 15<sup>th</sup> beat) from lying to standing is  $\geq 1.04$ , borderline is between 1.01- 1.03 and  $\leq 1.0$  is abnormal. In our study, the mean HR ratio of male cases is  $0.88 \pm 0.03$  and mean HR ratio of male controls is  $1.08 \pm 0.04$ . When compared, it was found significantly lesser ( $p < 0.05$ ; Fig 3 and 4). The 30 : 15 ratio of control was also compared with the international normative value ( $\geq 1.04$ ) and was not significantly different.

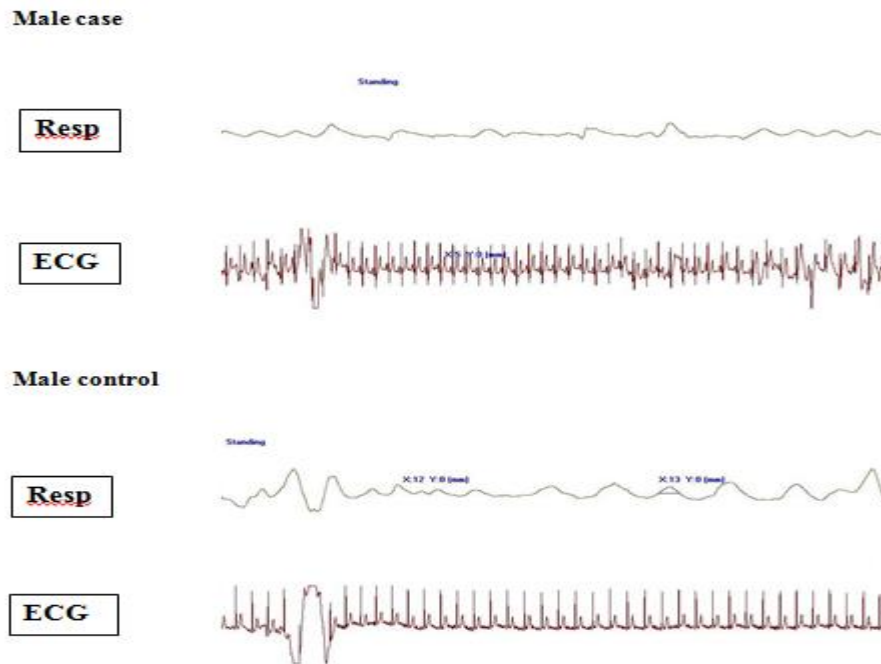


Figure-3 Original tracings showing heart rate changes during Tilt Table Testing in male cases and male controls. Speed = 15 mm/s, Sensitivity = 500  $\mu$ v for respiration and 50  $\mu$ v for ECG.

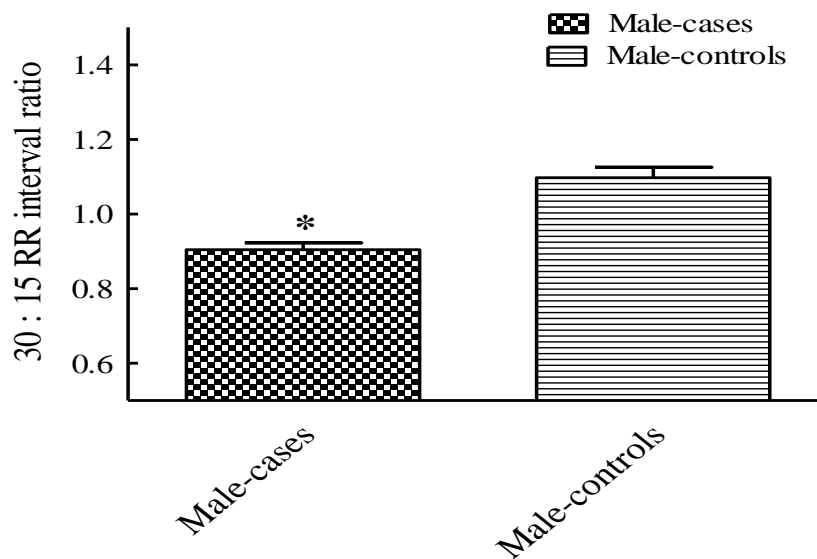
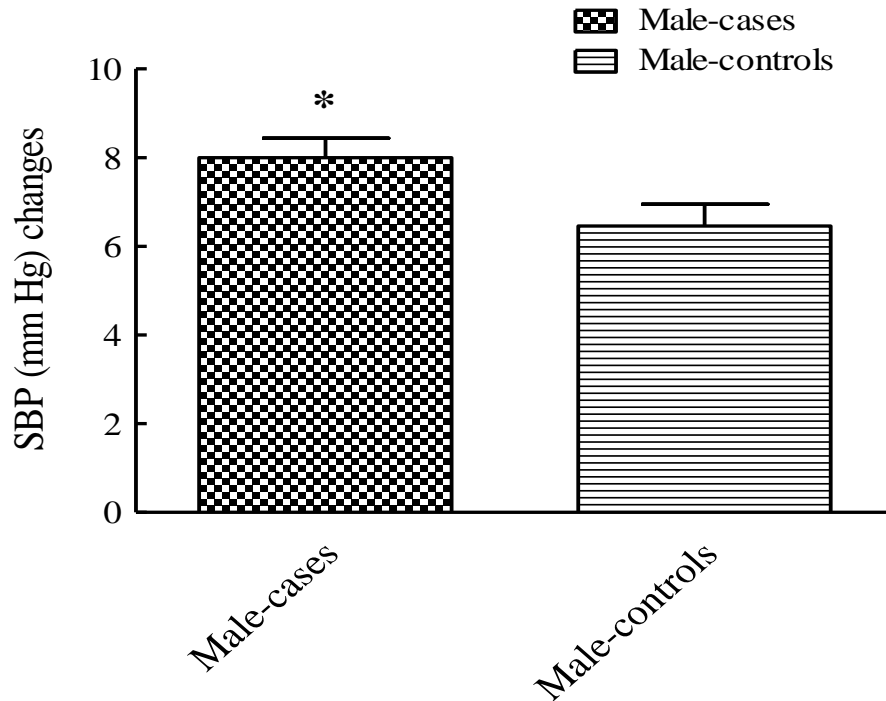


Figure-4 The histogram showing HR changes (30:15 Ratio) during Tilt Table Test in male cases and male controls. Data represents the mean  $\pm$  SEM value of male cases and male controls. An asterisk "\*" indicates  $p < 0.05$  as compared to the controls.

**Changes in Systolic Blood Pressure**

The normative international SBP response in lying to standing is  $\leq 10$  mm Hg, borderline is between 11-20 mm Hg and  $\geq 30$  mm Hg is abnormal. In our study the change in mean SBP in lying to standing of male cases is  $8.6 \pm 0.89$  mm Hg and male controls is  $6.5 \pm 0.76$  mm Hg. When compared, it was found significantly greater than the control ( $p < 0.05$ ; Fig 3 and 5). The SBP changes of male controls ( $6.5 \pm 0.76$  mm Hg) was also compared with the international normative value of SBP changes ( $\leq 10$  mm Hg) and was found within normal range.



**Figure-5** The histograms showing Systolic Blood Pressure change during Tilt Table Test in male cases and male controls. Data represents the mean  $\pm$  SEM value of changes in Systolic Blood Pressure of male cases and male controls. An asterisk “\*” indicates  $p < 0.05$  as compared to the controls.

**DISCUSSIONS**

The functions of the receptors can be tested by monitoring the changes in pulse and BP that occurs in response to brief period of straining [11]. In Valsalva maneuver (VM), the ratio of longest R-R interval within 20 beats of ending the maneuver to shortest interval during manoeuvre was taken. During manoeuvre, intrathoracic pressure is increased and the overall parasympathetic outflow of the body is decreased. As the increased intrapulmonary pressure causes the excitation of stretch receptors in the lung and the nerve impulses generated converges on the cardio-inhibitory area in the medulla. As a consequence, the parasympathetic outflow to the visceral organs is decreased. Since, heart is also receiving the parasympathetic innervations, therefore, the decreased parasympathetic supply leads to decreased R-R interval and thereby resulting tachycardia. When the glottis is open and the intrathoracic pressure returns to normal, cardiac output is restored but the peripheral vessels still remain constricted. The BP rises above normal and this stimulates baroreceptors, causing the increased RR interval thereby causing bradycardia.

In this study, the male cases had significantly lower Valsalva ratio as compared to the male controls indicating decreased parasympathetic reactivity / increased sympathetic reactivity. Sustained stimulation of the nociceptors might be the cause for the shifting of sympathovagal balance towards sympathetic side in the patients suffering with the chronic pain. If we compare the Valsalva ratio of male cases with the international value of Valsalva ratio ( $> 1.21$ ), it is again lesser indicating the shifting of sympathovagal balance towards the sympathetic side. If we compare the Valsalva ratio of controls versus the international normative value, it is

greater but not significant indicating increased parasympathetic activity in the normal population in comparison to the international standard.

Various researches have proposed a number of mechanisms for postural orthostatic tachycardia syndrome including hypovolemia [12-14], leg venous pooling [15], partial sympathetic denervation and hypersensitivity of cardiac receptors [16]. Thus, such patients have often been described as having a dysautonomia. Assumption of the standing position after supine rest for 30 min results in venous pooling and a transient decrease in cardiac output eliciting reflex activation of the sympathetic nervous system and a withdrawal of cardiac parasympathetic tone. This is reflected by characteristic changes in heart rate which increases abruptly towards a primary peak at around 3 sec, increases further to a secondary peak at around 12 sec. It then declines to a relative bradycardia at about 20 sec and then gradually rises again [17]. In tilt table test the HR changes and SBP changes from lying to standing were observed. In the cases, 30 : 15 ratio was found significantly lesser than the male controls. This is indicative of decreased parasympathetic / increased sympathetic reactivity in the cases in comparison to the controls. In this study, the HR changes occurring after Tilt Table Test are similar to the HR changes occurring during Valsalva maneuver which is further supporting that there is decrease in parasympathetic reactivity in the patients suffering with chronic pain. The above findings are consistent with the work performed on the chronic pain by using hand grip test and deep breath test elsewhere [18]. While comparing with the international normative value, the ratio is still significantly lesser in male cases. The 30 : 15 ratio in controls are greater than the international normative value indicating the increased parasympathetic / decreased sympathetic activity in the normal population of this reason in comparison to the international standard.

#### CONCLUSION

In conclusion, the Valsalva ratio in the cases are decreased indicating the decreased parasympathetic / increased sympathetic reactivity which is further supported by the 30 : 15 ratio observed during Tilt Table Test. The increase in SBP in cases also supports the shifting of sympathovagal balance towards the sympathetic side.

#### REFERENCES

- [1] Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neuroscience and Biobehavioral Reviews*. 2004; 28: 395–414.
- [2] Birklein F, Riedl B, Claus D, Neundtfer B. Pattern of autonomic dysfunction in time course of complex regional pain syndrome; *Clinical Autonomic Research* 1998; 8:79-85.
- [3] Fazalbhoy A, Birznieks I, Vaughan G. Macefield; Individual differences in the cardiovascular responses to tonic muscle pain: parallel increases or decreases in muscle sympathetic nerve activity, blood pressure and heart rate. *Exp Physiol* 2012; 97(10): 1084–1092.
- [4] Nilsen KB, Sand T, Westgaard RH et al., Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *European Journal of Pain*. 2007;11(7):743–755.
- [5] Bäcker M, Grossman P, Schneider J et al. Acupuncture in migraine: investigation of autonomic effects. *Clinical Journal of Pain* 2008; 24 (2):106–115.
- [6] Shiro Y, Arai YCP, Matsubara T, Isogai S, Ushida T. Effect of muscle load tasks with maximal isometric contractions on oxygenation of the trapezius muscle and sympathetic nervous activity in females with chronic neck and shoulder pain. *BMC Musculoskeletal Disorders* 2012; 13: 146-152.
- [7] Folta A, Metzger BL, Therrien B. Preexisting physical activity level and cardiovascular responses across the Valsalva maneuver. *Nurs Res* 1989; 38:139–143.
- [8] Freeman R. Noninvasive evaluation of heart rate variability: the time domain. In: Low PA (ed) *Clinical Autonomic Disorders*, 2nd edn. Lippincott-Raven, Philadelphia 1997; pp 297–307.
- [9] Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T (1986) Effects of age and blood pressure on the cardiovascular responses to the Valsalva maneuver. *J Am Geriatr Soc* 1986; 34: 431–434.
- [10] van Dijk JG, Koenderink M, Zwinderman AH, Haas J, Kramer CGS, den Heijer JC. Autonomic nervous system tests depend on resting heart rate and blood pressure. *J Auton Nerv Syst* 1991; 35: 15–24.
- [11] Ganong's Review of Medical Physiology, 24<sup>th</sup> Edition, published by Tata McGraw Hill Education Private Limited, 2012; 593.



- [12] Fouad FM, Tadena-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. *Ann Intern Med* 1986, 104: 298–303.
- [13] Jacob G, Robertson D, Mosqueda-Garcia R, Ertl A, Robertson R, Biaggioni I. (1997) Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. *Am J Med* 1997; 103: 128–133.
- [14] Raj SR, Biaggioni I, Yamhure PC, Black BK, Paranjape SY, Byrne DW, Robertson D. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation* 2005; 111: 1574–1582
- [15] Low P, Opfer-Gehrking T, Textor S, Benarroch E, Shen W, Schondorf R, Suarez G, Rummans T. Postural tachycardia syndrome (POTS). *Neurology* 1995; 45(4 Suppl): S19–S25.
- [16] Russo V, Crescenzo I, Ammendola E, Santangelo L, Calabro R. Sympathovagal balance analysis in idiopathic postural orthostatic tachycardia syndrome. *Acta Biomed* 2007; 78: 133–138.
- [17] Malik M. *Clinical Guide to Cardiac Autonomic Tests*. Kluwer Academic Publishers, Netherlands 1998; 51-52.
- [18] Roy A, Singh SK. Evaluation of cardiovascular autonomic control in chronic pain patients using isometric handgrip and deep breath maneuvers. *National Journal of Physiology, Pharmacy and Pharmacology* 2016;6(5):420-426.