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# CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN PATIENTS OF ORTHOSTATIC HYPOTENSION

**Tripathi Sumeet** MD Associate Professor Department of Physiology Chhattisgarh Institute of Medical Sciences Bilaspur, Chhatisgarh

**Khandelwal Ekta*** MD Associate Professor Department of Physiology All India Institute of Medical Sciences Raipur, Chhattisgarh *Corresponding Author

**ABSTRACT** The autonomic dysfunction is an important cause of orthostatic hypotension. The patients of orthostatic hypotension may or may not be symptomatic. The study was conducted to evaluate cardiovascular autonomic status in patients of orthostatic hypotension. The study was conducted in 15 patients of orthostatic hypotension and 15 age matched subjects. The heart rate variability was assessed from 5 min resting supine ECG. The parasympathetic and sympathetic autonomic reactivity was assessed using Ewing's battery of tests. The heart rate variability and measures of autonomic reactivity were lower in the patients with orthostatic hypotension as compared to control. The parasympathetic component of the heart rate variability and reactivity test was most affected in patients. The autonomic dysfunction is common in patients of orthostatic hypotension. The autonomic profile of symptomatic patients is not different from that of asymptomatic patients indicating that additional deficits of cerebral autoregulation play a crucial in development of symptoms.

**KEYWORDS :** orthostatic hypotension, heart rate variability

## INTRODUCTION

Orthostatic hypotension or Postural hypotension is defined as "a systolic blood pressure decrease of at least 20 mmHg or a diastolic blood pressure decrease of at least of 10 mmHg within 3 minutes of standing up".[1] Symptoms like dizziness, light-headedness', weakness, blurred vision, impaired concentration, and loss of consciousness are seen in patients when on standing.[2,3]

The etiology of orthostatic hypotension includes neural and non-neural factors.[4] Autonomic abnormality in 19 of 42 patients using objectives tests of autonomic function like Valsalva manoeuvre, deep breathing test and cold pressor test has been reported.[5] More, autonomic dysfunction was reported in 99 out of 100 consecutive patients irrespective of aetiology or comorbid conditions.[6]

Heart rate variability is an important indicator of autonomic control of the heart. [7] Low heart rate variability has been reported in time domain as well as frequency domain in patients of orthostatic hypotension with known dysautonomia. [8] Low sympathetic component has been shown in patients of Parkinson's disease with orthostatic hypotension. [9] In all the above studies, the patients of orthostatic hypotension were treated as one group irrespective of symptoms.

In the present study, the cardiovascular autonomic function was quantified by a standard battery of autonomic function test and heart rate variability in patients of orthostatic hypotension and compared with apparently healthy controls.[10,11]

## MATERIAL AND METHOD

### Subjects

The study was conducted in the Autonomic function laboratory of the Department of Physiology, All India Institute of Medical Sciences, Raipur after obtaining ethical clearance from the Institutional ethical committee. The patients were recruited from out-patient department of the hospital and the age and sex match controls were recruited from the general population. The diagnosis of orthostatic hypotension was confirmed in the laboratory by measuring the maximal fall in blood pressure within 3 minutes of standing .[12] The patients were labelled as symptomatic if they had any history of fall, black out or dizziness on standing. Control subjects had no history of any symptom on standing from reclining posture. Patients with severe medical or orthopaedic disability or with known cognitive disorders were excluded from the study. The patients and control subjects were explained the procedure and informed consent was obtained. The patients were given instruction to abstain from tea or coffee 24 hour prior to testing. They were asked to take light breakfast at least 2 hours before testing. All the tests were conducted in the morning hours in between 9:00 to 12:00 h in a quiet room with temperature of 25 Celsius.

Resting blood pressure was measured after ensuring a rest period of 15 minutes to the patients and controls. The blood pressure was recorded from the right arm using a standard mercury sphygmomanometer. The heart rate measurement was done from the lead II electrocardiographic (ECG) recordings and respiration was monitored with stethographic tracings recorded on the digital polygraph (AD Instruments, Australia). Sympathetic reactivity was assessed by diastolic blood pressure response during handgrip test and cold pressor test. The parasympathetic reactivity was assessed by expiration to inspiration ratio (E:I ratio) during deep breathing test, Valsalva ratio (VR) during Valsalva manoeuvre, 30:15 ratio during head up tilt.

**Deep breathing test**: A baseline recording of ECG and respiration was done for 30 seconds in sitting posture. The patient was visually guided to breathe slowly and deeply at 6 cycles per minute. The E:I ratio was calculated from largest RR interval (one R wave to next R wave of ECG) during expiration and smallest RR interval during inspiration. The E:I ratio of > 1.21 was considered normal.

**Valsalva test:** The baseline ECG and respiration was done for 30 seconds in sitting posture. The subject was instructed to blow into a mouth piece attached to sphygmomanometer to raise the pressure to 40 mmHg for 15 seconds. The Valsalva ratio (VR) was calculated from maximal RR interval during phase IV and smallest RR interval during phase II. The VR ratio > 1.21 was considered normal.

**Cold pressor test:** The baseline blood pressure was measured. The subjects hand was immersed into cold water (10 C for 1 minute) and change in blood pressure at the end of the 1 minute was measured. A rise of more than 10 mmHg in diastolic blood pressure was considered normal.

**Handgrip test:** The baseline blood pressure was measured. The subject was asked to press the hand grip dynamometer at 30% of their maximum voluntary contraction for 4 minutes. The change in blood pressure during test was measured. A rise of more than 10 mmHg in diastolic blood pressure was considered normal.

**Lying to standing test:** The supine blood pressure was measured and the subjects were asked to acquire standing position in 3 seconds. The maximum fall within 3 minutes of orthostasis was noted. The 30:15 ratio was calculated from maximum RR interval at around 30 seconds and minimum RR interval at around 15 seconds. A fall less than 10 mmHg and 30:15 ratio more than 1.04 was considered normal.

**Heart rate variability :** The subjects was asked to lie down quietly for 15 minutes in a quiet room. The temperature of the room was maintained at 25°C and subjects was instructed to close the eyes and to avoid talking, moving hands, legs and body, coughing during test. The ECG was recorded for 5 minutes and analysed by Labchart software (ADI, Australia).

**Time domain analysis:** The following parameters were selected for the analysis:

1. **SDNN** - Standard deviation of all RR intervals. It is mathematically equal to the total power of the spectral analysis.
2. **PNN50** - the number of interval difference of the successive RR intervals greater than 50 ms of RR intervals divided by the total number of RR intervals.
3. **SDSD** - Standard deviation of differences between adjacent RR intervals.

**Frequency domain analysis:** The spectral power density of the different component frequencies in the heart rate was carried out by the fast Fourier transform. Power spectral densities were computed using Hamming window in three frequency bands: Very Low Frequency (0.001 – 0.05), Low Frequency (0.05 – 0.15 Hz) and High Frequency (0.15 – 0.40 Hz) and were normalized for total power.

**Statistical analysis**

The data were analyzed SPSS software package version 11.5 (SPSS Inc., Chicago, USA). The unpaired't' test and Mann-Whitney U test was used for quantitative data and Fisher's exact test was used for categorical data.

## RESULTS

The cardiovascular reactivity and heart rate variability was quantified in 15 patients and 15 age and sex matched control subjects. 7 patients were classified as symptomatic, out of these two patients reported dizziness during lying to standing test and 8 asymptomatic patients. There is no significant difference between age, gender distribution, resting blood pressure of the patients and control subjects.

The fall in systolic blood pressure during head up tilt confirmed the diagnosis of orthostatic hypotension in the patients (30.93 + 8.71 mmHg). The supine systolic blood pressure was significantly higher in the patients as compared to the control subjects.

The table 1 shows the quantitative values of the different tests of parasympathetic and sympathetic reactivity in patients and control subjects. All the tests for parasympathetic and sympathetic reactivity showed lower values in the patients as compared to control subjects.

To investigate the relationship between status of autonomic dysfunction and symptoms, the patients were sub-grouped as symptomatic and asymptomatic. The results of the autonomic tests in symptomatic and asymptomatic are shown as quantitative values in table 2. The symptomatic and asymptomatic group did not differ for the results of autonomic reactivity.

Heart rate variability : The table 3 shows various parameters of heart rate variability in time domain and frequency domain in patients and control subjects. The patients group showed significantly lower variability in time domain and lower absolute power in frequency domain. The subgroup analysis showed no difference between the symptomatic and asymptomatic patients either in time domain or frequency domain except in SDSD and total power where it was noted that asymptomatic group had lower values as compared to the symptomatic group.

## DISCUSSION

The present study was conducted to quantify the cardiovascular autonomic function in the patients of orthostatic hypotension and to investigate the relationship between the status of cardiovascular autonomic function with presence and absence of symptoms in the patients.

The supine systolic blood pressure was higher in the patients. Similar observations have been reported earlier. [13,14,15] It has been proposed that higher systolic pressure and higher cardiac output is compensatory response to ensure adequate cerebral perfusion on attainment of upright posture. [14]

The parasympathetic and sympathetic reactivity was found to be lower in patients as compared to controls. The parasympathetic reactivity was abnormal in 13 (86.66 %) patients while sympathetic reactivity was abnormal in 7 (46.66 %) of patients. The percentages are higher than those reported by Ward et al. who found sympathetic abnormality in 20% and parasympathetic abnormality in 30% of patients and lower than those reported by Ejaz et al. [6,5] The tests of parasympathetic reactivity are based on heart rate response to different manoeuvres while the tests of sympathetic reactivity are based on the diastolic blood pressure response to manoeuvres. Thus, it appears that loss of autonomic control of the heart rate is an early contributor in the development of orthostatic hypotension. This is also reflected in lower heart rate variability (SDNN in time domain and absolute power in the frequency domain) in the patients. Time domain parameters like SDNN and pNN50 clearly show that parasympathetic tone is diminished in these patients. Hilz et al. have also reported lower SDNN in time domain. The lower resting parasympathetic tone has been postulated to be an important feature in pathophysiology of orthostatic hypotension. Loss of parasympathetic tone diminishes the initial cardio-acceleratory response to standing that occurs due to vagal withdrawal, leading to failure in maintenance of blood pressure. Loss of heart rate response to fluctuations in the blood pressure pre-disposes to the development of orthostatic hypotension. Diminished heart rate response in the elderly at the onset of orthostatic challenge has been reported and it has been proposed that it may be related to vagal dysfunction, [16]. Interestingly we found that symptomatic patients tended to have higher values of HRV as compared to asymptomatic. The median LF:HF ratio was 1.32 in symptomatic as compared to 0.78 in asymptomatic. The difference was not statistically significant perhaps due to small size but it points towards the greater loss of parasympathetic tone in symptomatic patients. The higher HRV values could indicate large blood pressure fluctuations in symptomatic patients. Larger fluctuations in the blood pressure have been reported in patients of orthostatic hypotension. [17] Measurement of blood pressure variability in patients of orthostatic hypotension will be useful in testing this hypothesis.

The symptoms on orthostasis occur due to decrease in cerebral perfusion. This can happen either due to large fall in blood pressure to a value below the autoregulatory range of cerebral circulation or dysfunctions in the cerebral autoregulation. We subgrouped the patients into symptomatic and asymptomatic on the basis of history of symptoms on orthostasis. The fall in the systolic blood pressure was similar in the two groups which are well within the normal autoregulatory range of cerebral circulation, [18]. The loss of autonomic reactivity and heart rate variability was also similar in the two groups. Thus, it is likely that symptomatic patients have dysfunction in cerebral autoregulation. Loss of cerebral autoreguation in 5 of 21 patients of orthostatic hypotension has been reported but without any reference to the symptoms. [15] Pooling of blood in normal subjects can lead to downward shift in the autoregulatory range of cerebral perfusion. [18]

We conclude that dysfunction in autonomic control of cardiovascular system is common feature in patients of orthostatic hypotension with parasympathetic loss more prevalent than sympathetic loss. The findings needs to be confirmed with higher number of subjects in the symptomatic and asymptomatic group along with estimation of the cerebral autoregulation.

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**Table 1 Parasympathetic and sympathetic reactivity test in patients and control subject.**

| Parameters | Patients (n = 15) | Controls (n = 15) | p value |
|---|---|---|---|
| Test of parasympathetic reactivity | | | |
| E:I | 1.11 (1 -1.16) | 1.35 ( 1.23-1.4) | 0.001 |
| VR | 1.19 (1.03 -1.73) | 1.72 (1.34 – 2.14) | 0.015 |
| 30:15 | 1.04 (1 – 1.15) | 1.25 (1.18 – 1.41) | 0.005 |
| Test of sympathetic reactivity | | | |
| HGT ΔDBP (mmHg) | 10 (4 -16) | 18 ( 12 -22) | 0.005 |
| CPT ΔDBP (mmHg) | 10 (4 -12) | 16 (10 – 20) | 0.006 |

Data is presented as median (interquartile range). Mann-Whitney U test was applied.

**Table 2 Parasympathetic and sympathetic reactivity test in symptomatic and asymptomatic patients.**

| Parameters[a] | Symptomatic (n = 7) | Asymptomatic (n = 8) | p value |
|---|---|---|---|
| Test of parasympathetic reactivity | | | |
| E:I | 1.11 (1.03 – 1.20) | 1.10 (1.04 – 1.55) | 0.95 |
| VR | 1.39 (1.04 – 1.85) | 1.19 (1.01 – 1.45) | 0.56 |
| 30:15 | 1.07 (1.00 – 1.41) | 1.00 (1.00 – 1.12) | 0.23 |

| Test of sympathetic reactivity | | | |
|---|---|---|---|
| LST ΔSBP | 28 (20 – 30) | 28 (24 – 36) | 0.48 |
| HGT ΔDBP (mmHg) | 6 (0 – 14) | 10 (8.5 – 19.5) | 0.14 |
| CPT ΔDBP (mmHg) | 8 (0 – 10) | 10 (6.5 – 16.5) | 0.22 |

Data is presented as median (interquartile range). Mann-Whitney U test was applied.

**Table 3 Heart rate variability in patients and control subjects.**

| Parameters | Patients (n = 15) | Controls (n = 15) | p value |
|---|---|---|---|
| Time domain | | | |
| SDNN (ms) | 12.96 (10.47-34) | 35.69 (24.40-42.31) | 0.02 |
| pNN50 (%) | 0.00 (0.00-4.35) | 6.70 (0.31- 10.59) | 0.02 |
| SDSD (ms) | 14.30 (8.38-29.91) | 35.12 (26.04-43.71) | 0.02 |
| Frequency domain | | | |
| LF/HF (n.u.) | 0.911 (0.354-2.26) | 0.767 (0.25-2.01) | 0.47 |
| LF power (n.u.) | 36.46 (23.75-60.49) | 35.74 (18.87-62.59) | 0.85 |
| HF power (n.u.) | 43.82 (23.71-67.05) | 50.50 (31.34-75.33) | 0.25 |
| Total power (ab) | 292.47 (155.57-1116.50) | 1289.98 (599.24-2385.37) | 0.04 |

Data is presented as median (interquartile range). Mann-Whitney U test was applied. (n.u. = normalized units, ab = absolute).

## REFERENCE


1. Harms M, Colier W, Wieling W, Lenders J, Secher N, Lieshout J. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. Stroke 2000; 3:1608-14.
2. Bradley JG, Davis KA. Orthostatic hypotension. Am Fam Physician 2003; 68:2393-8.
3. Goldstein DS, Pechnik S, Holmes C, Eldadah B, Sharabi Y. Association between supine hypertension and orthostatic hypotension in autonomic failure. Journal of American heart association 2003; 42: 136-42.
4. Task force. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93:1043-65.
5. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 2006; 13:930-6.
6. Mathias CJ, Bannister R. Investigations of autonomic disorders. In : Mathias CJ, Bannister R, editors. Autonomic failure, A Text Book of Clinical Disorders of Autonomic Nervous System. 4th ed. Oxford: Oxford University Press; 1999.pp.169 – 95.
7. Ward C, Kenny RA. Reproducibility of orthostatic hypotension in symptomatic elderly. American journal of medicine 1996; 100:418-22.
8. Ejaz AA, Haley WE, Wasiluk A, Meschia JF, Fitzpatrick PM. Characteristics of 100 consecutive patients presenting with orthostatic hypotension.Mayo Clin Proc 2004;79:890-4.
9. Novak V, Novak P, Spies JM, Low PA. Autoregulation of cerebral blood flow in orthostatic hypotension. American heart association 1998; 29: 104-11.
10. Gupta V, Lipsitz LA. Orthostatic hypotension in elderly: diagnosis and treatment. Am J Med 2007; 120: 841–7.
11. Hilz MJ, Axelrod FB, Haertl U, Brown CM, Stemper B. Transcranial Doppler sonography during head up tilt suggests preserved central sympathetic activation in familial dysautonomia. J Neurol Neurosurg. Psychiatry 2002; 72: 657-60.
12. Barbic F, Perego F, Canesi M, Gianni M, Biagiotti S, Costantino G et al.Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. Hypertension 2007; 49:21-2.
13. Hohnloser SH, Klinenheben T. Basic autonomic tests. In : Marek Malik, editor. Clinical guide to cardiac autonomic test. Kluwer Academic Publisher London; 1998; pp.51–65.
14. Robertson D. The pathophysiology and diagnosis of orthostatic hypotension. Clin Auton Res 2008; 18: 2-7
15. Ejaz AA, Kazory A, Heinig ME. 24-hour blood pressure monitoring in the evaluation of supine hypertension and orthostatic hypotension. J Clin Hypertens 2007; 9:952-55.
16. Shi X, Wray DW, Formes KJ, Wang HW, Hayes PM, O-Yurvati AH et al. Orthostatic hypotension in aging humans. Am J Physiol 2000; 279: 1548 - 54.
17. Guo H, Tierney N, Schaller F, Raven PB, Smith SA, Shi X. Cerebral autoregulation is preserved during orthostatic stress superimposed with orthostatic hypotension. J Appl Physiol 2006; 100: 1785- 92.
18. Gehrking JA, Hines SM, Benrud-Larson LM, Opher-Gehrking TL, Low PA.What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension? Clin Auton Res 2005; 15:71-5.