Cardiovascular autonomic functions & cerebral autoregulation in patients with orthostatic hypotension

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Background & objectives: Patients of orthostatic hypotension may or may not have symptoms of the cerebral hypoperfusion despite fall in the blood pressure. The present study was done to quantify autonomic functions and cerebral autoregulation in patients of orthostatic hypotension with or without symptoms.

Methods: The study was conducted in 15 patients of orthostatic hypotension and 15 age, sex matched control subjects. The sympathetic reactivity was measured by diastolic blood pressure response to handgrip test (ΔDBP in HGT) and cold pressor test (ΔDBP in CPT). The parasympathetic reactivity was measured by E:I ratio during deep breathing test (DBT) and Valsalva ratio (VR) during Valsalva maneuver. The cerebral autoregulation was computed from the changes in the cerebral blood flow, cerebrovascular conductance and blood pressure measured during different time points during head-up tilt (HUT).

Results: The sympathetic reactivity was lower in patients as compared to controls [ΔDBP in HGT: 10 (4 - 16) vs 18 (12 - 22) mmHg, *P*<0.01; ΔDBP in CPT : 10 (4-12) vs 16 (10-20) mmHg, *P*<0.01]. The parasympathetic reactivity was also lower in patients as compared to controls. The sympathetic and parasympathetic reactivity was comparable in the symptomatic and asymptomatic patients. The maximum fall in blood pressure during HUT was comparable between symptomatic and asymptomatic patients (29.14 ± 10.94 vs 29.50 ± 6.39 mmHg), however, the percentage fall in the cerebral blood flow was significantly higher in the symptomatic (*P*<0.05) compared to asymptomatics.

Interpretation & conclusions: Patients with orthostatic hypotension had deficits in sympathetic and parasympathetic control of cardiovascular system. Cerebral autoregulation was present in asymptomatic patients (increase in cerebrovascular conductance) during HUT while it was lost in symptomatic patients.

Attainment of upright posture from a supine posture is associated with pooling of blood in the lower part of the body[1]. Orthostatic hypotension is diagnosed with the fall in blood pressure on orthostasis by more than 20 mmHg in systolic blood pressure or more than

10 mmHg in diastolic blood pressure within three minutes[2]. However, orthostatic hypotension is not always associated with symptoms. Symptoms such as dizziness, lightheadedness, weakness, blurred vision, impaired concentration, and loss of consciousness

are seen in patients when the cerebral perfusion is compromised[3]. Orthostatic hypotension occurs in all ages but it is more common in the elderly, especially in patients with dysfunctions of autonomic nervous system and/or with hypovolemia[4].

Dysregulation of autonomic functions directly or indirectly contributes to the aetiology of the orthostatic hypotension[5]. Most patients of orthostatic hypotension are asymptomatic and those who experience symptoms usually show large fall in blood pressure on orthostasis leading to cerebral hypoperfusion[6]. However, in many cases even a small fall in blood pressure is associated with relatively larger decrease in cerebral perfusion leading to occurrence of symptoms[7]. Impaired cerebral autoregulation has been suggested to underlie the occurrence of symptoms in patients of orthostatic hypotension[7,8]. Impaired cerebral autoregulation acts over and above the autonomic dysfunction in development of symptoms in patients of orthostatic hypotension. Despite suggestion of specific testing of autonomic function for detecting sub-clinical orthostatic hypotension only a few studies have addressed this aspect[9,10].

The present study was done to quantify autonomic functions and the cerebral autoregulation in patients of orthostatic hypotension and in healthy subjects. Cerebral autoregulation was also compared between symptomatic and asymptomatic patients.

Material & Methods

The study was conducted in the Autonomic Function Laboratory of the Department of Physiology, All India Institute of Medical Sciences, New Delhi during December 2006 - April 2008, after obtaining ethical clearance from the Institutional Ethics Committee. The patients were referred from out-patient departments of endocrinology and medicine of the hospital for routine testing of the autonomic function by the physician, while the age and sex match controls were recruited from the staff of the hospital. Of the 15 patients included in the study, only two were referred with specific diagnosis of orthostatic hypotension while in others the presence of orthostatic hypotension was revealed during the assessment of autonomic function. On the basis of detailed history, seven patients had symptoms of orthostatic in past while eight were asymptomatic. The diagnosis of orthostatic hypotension was made in the laboratory by measuring the fall in blood pressure within 3 min of postural challenge as per the criteria of American Autonomic Society and the American Academy of Neurology 1996[11], EFNS Task Force

2006[2]. Out of 35 patients who were diagnosed as having orthostatic hypotension 20 were excluded due to orthopedic disability, history of epilepsy or due to known cognitive disorders. 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 h and stop medications (2 patients) likely to affect the autonomic testing 48 h prior to day of testing. They were asked to take light breakfast at least 2 h before testing. All the tests were conducted in the morning hours in a quiet room with temperature of 25°C.

Resting parameters like blood pressure, heart rate and cardiac output were measured after ensuring a rest period of 15 min to the patients. The blood pressure was recorded from the right arm using a standard mercury sphygmomanometer. The heart rate and respiration monitoring was done from the ECG recordings and stethographic respiratory tracings recorded on the polygraph (POLYRITE-4, Recorders and Medicare System, India). Cardiac output was estimated using non-invasive cardiac output monitor (NICOMON, Larsen and Tubro, India). Standard battery of test was used for assessment of sympathetic and parasympathetic reactivity[12]. Sympathetic reactivity was assessed by systolic blood pressure response during lying to standing, head up tilt (HUT) and diastolic blood pressure response during handgrip test and cold pressor test (CPT). The parasympathetic reactivity was assessed by E:I ratio (expiration to inspiration) during deep breathing test (DBT), Valsalva ratio during Valsalva maneuver (VM), 30:15 ratio during lying to standing and head up tilt.

Protocol of tests:

Lying to standing test (LST) - The supine blood pressure was measured and the subject was asked to acquire standing position in 3 sec. The maximum fall of systolic blood pressure within 3 min of orthostasis was noted.

Head up tilt (HUT) - Subject was asked to lie down on a head up tilt table for 5 min and the supine blood pressure was measured. The table was tilted with in 15 sec for 70º (4.8 deg/sec) and kept in that position for 5 min. The subjects were asked to stand on the foot rest (passive standing). The maximum fall within 3 min of orthostasis was noted.

The 30:15 ratio was calculated from maximum RR interval at around 30 sec and minimum RR interval at around 15 sec. A fall less than 10 mmHg in systolic

blood pressure and 30 : 15 ratio more than 1.04 was considered normal.

Deep breathing test (DBT) - A baseline recording of ECG was done for 30 sec. 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 during expiration and smallest RR interval during inspiration. The average value of 6 cycles was computed for each subject. E: I ratio of >1.21 was considered normal.

Valsalva manoeuvre (VM) - The baseline ECG was recorded. The subject was instructed to blow into a mouth piece attached to sphygmomanometer to raise the pressure to 40 mmHg for 15 sec. The Valsalva ratio was calculated from maximal RR interval during phase IV and smallest RR interval during phase II. VR ratio >1.21 was considered normal.

Cold pressor test (CPT) - The baseline blood pressure was measured. The subjects hand was immersed into cold water (10°C for 1 min) and rise in diastolic blood pressure at the end of the 1 min was measured. A rise of 10 mmHg in diastolic blood pressure was considered normal.

Handgrip test (HGT) - The baseline blood pressure was measured. The subject was asked to hold the hand grip dynamometer at 30 per cent of their maximum voluntary contraction (MVC) for 4 min. The rise in diastolic pressure during test was measured. A rise of more than 10 mmHg in diastolic blood pressure was considered normal.

Cerebral blood flow was assessed by noninvasive method using Rheoencephalograph (RHEOSCREEN® COMPACT, Medis, Germany) during HUT. The change in the impedance offered by a segment of the body is proportional to the flow of blood within that segment[13]. The rheoenchephalography method has been validated against Laser doppler flow and carotid flow in animals and strain-gauge plethysmography in human subjects[14,15]. The Rheoencephalography method has been employed in human studies for estimation of cerebral perfusion[16,17]. In this method electrodes are placed according to 10-20 system. Six standard silver disc electrodes of 0.5 cm diameter were used. The current injecting electrodes I_1 and I_2 placed on nasion and inion and voltage sensing electrodes F1-O1 and F2-O2 on left and right side respectively were placed in frontal and occipital regions of scalp one on each side. The ECG is simultaneously acquired to synchronize

the changes in impedance with each heart beat and it is averaged over 10 sec for computing the cerebral blood flow.

Subjects were allowed to rest in supine position for 10 min. Then 70º (4.8 deg/sec) HUT was given with the help of a motorized table within 15 sec and kept in that position for five minutes. The cerebral blood flow was measured between these electrodes after 0.5, 1, 3 and 5 min during HUT. The change in cerebral blood flow and cerebrovascular conductance were calculated.

Statistical analysis: Each parameter was tested for distribution of data. In case of data distribution being normal, parametric tests were applied and otherwise appropriate non-parametric tests were applied. The following tests were used: Paired and unpaired 't' test, Mann Whitney U test, Repeated measures ANOVA with Bonferronni correction, Friedman and Wilcoxon signed ranks test as appropriate for the data.

Results

Thirty five patients of orthostatic hypotension were referred to the Autonomic Function Laboratory for recruitment in the study over a duration of 18 months (from December 2006 to April 2008). Only 15 patients were selected after exclusion and consent. The diagnosis of orthostatic hypotension was confirmed in the laboratory as per criteria laid by the American Academy of Neurology (1996)[11] and EFNS Task Force (2006)[2]. Fifteen age matched and sex matched healthy subjects were recruited for the study as controls.

The patients of orthostatic hypotension had higher supine systolic blood pressure and resting cardiac output, cardiac index as compared to the controls. The diastolic blood pressure, body mass index (BMI) and heart rate were comparable between the patients and the control (Table I). All the parameters for parasympathetic and sympathetic reactivity were lower in the patients as compared to control subjects (Table II). The sub-group analysis of symptomatic and asymptomatic patients showed no difference in the groups for any test of sympathetic or parasympathetic reactivity.

Cerebral blood flow and the blood pressure measurements were done during supine posture (baseline) and during head up tilt at 0.5, 1, 3 and 5 min in patients and control subjects. There was no difference in the baseline cerebral blood flow between the groups during supine posture. During postural challenge, the patients of orthostatic hypotension

Table I. Resting autonomic parameters of the orthostatic hypotension patients and controls (supine position)

Parameters	Patients (n = 15)	Controls (n =15)
Age (yr)	41.80 ± 12.86	42.07 ± 11.78
Male: female (n)	5:10	5:10
BMI (kg/m²)	25.30 ± 4.18	23.86 ± 2.65
Systolic blood pressure (mm Hg)	130.00 ± 15.82*	118.93 ± 13.26
Diastolic blood pressure (mm Hg)	82.53 ± 10.26	77.60 ± 8.39
Heart rate (per min)	78.67 ± 11.94	70.60 ± 13.22
Cardiac output (litre/min)	5.21 ± 1.27*	04.37 ± 0.57
Cardiac index (liter/min/m²)	3.17 ± 0.43*	2.78 ± 0.29

Data presented as mean ± standard deviation; *$P<0.05$ compared to controls

Table II. Parasympathetic and sympathetic reactivity test in patients and control subject

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

Data presented as median (interquartile range). E:I, expiration to inspiration ratio during deep breathing test; VR, Valsalva ratio during the Valsalva maneuver; 30:15 ratio on lying to standing test; ΔDBP, rise in diastolic pressure during HGT (hand grip test) and CPT (cold pressor test); *$P<0.01$, **<0.001 compared to controls

showed a significant reduction in cerebral blood flow at each time point with baseline value whereas in control group there was no significant difference from baseline value at all time points except at 5 min (Table III). The systolic and diastolic pressure decreased in the patients of orthostatic hypotension during HUT with maximal fall occurring by 3rd min (Table III).

In each patient, the relationship between the cerebral blood flow and systolic blood pressure response was quantified by taking paired values of cerebral blood flow and systolic blood pressure at 5 time points. Cerebral vascular conductance for each patient at each time was computed by dividing the cerebral flow with the systolic blood pressure at that point (Table IV). The average conductance for the symptomatic and asymptomatic patients at each time point is plotted against the systolic blood pressure at that time point (Fig. a and b). Increase in conductance with decrease in blood pressure during HUT is indicative of autoregulation (Fig. b).

In symptomatic patients, the cerebrovascular conductance remained unchanged throughout the HUT, *i.e.* proportional decrease in cerebral blood flow with fall in systolic blood pressure, indicative of loss of autoregulation of cerebral blood flow (Table IV, Fig. a). In asymptomatic patients, cerebrovascular conductance increased with decrease in systolic blood pressure during HUT, indicative of presence of autoregulation of cerebral blood flow (Table IV, Fig. b).

Additionally, the maximum fall in cerebral blood flow and systolic blood pressure during HUT was determined and the cerebral autoregulation was quantified as change in blood flow per unit fall in

Table III. Changes in cerebral blood flow blood flow, systolic blood pressure and diastolic blood pressure during HUT in patients and controls at different time points

Time Points (min)	Cerebral blood flow (ml/100 ml tissue/min)		Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	Patients (n=15)	Controls (n=15)	Patients (n=15)	Controls (n=15)	Patients (n=15)	Controls (n=15)
Baseline	33.46 (20.38-38.57)	31.30 (24.64-32.16)	130 ± 15.82	118.93 ± 13.26	82.53 ± 10.26	77.60 ± 8.39
0.5	28.35 (19.37-33.90)[a]	25.76 (23.51-31.44)	118.27 ± 17.43[a]	125.20 ± 16.33	80 ± 9.79	81.87 ± 9.33[a]
1	28.37 (17.86-36.62)[b]	24.43 (23.78-35.41)	109.73 ± 17.41[b]	126.8 ± 13.06	76 ± 9.22[a]	83.6 ± 8.07[b]
3	28.43 (17.86 -35.34)[c]	26.02 (22.58-34.11)	102 ± 15.38[c]	129.60 ± 13.11 [b]	74 ± 8.94[b]	88.13 ± 6.78[c]
5	25.40 (21-30.76)[d]	27.84 (21.59-32.31)[d]	105.2 ± 16.67[d]	125.47 ± 13.84	75.87 ± 9.18[c]	84.4 ± 5.86[d]
P value*	0.003	N.S.	0.001	0.004	0.001	0.001

Cerebral blood flow was analyzed using Friedman's test with Wilcoxon signed ranks test. The systolic and diastolic blood pressures were analysed by R-ANOVA with Bonferroni correction. *P value of Friedman's test and ANOVA. [a,b,c,d], significant difference from baseline in patients and controls at 0.5, 1, 3 and 5 min respectively
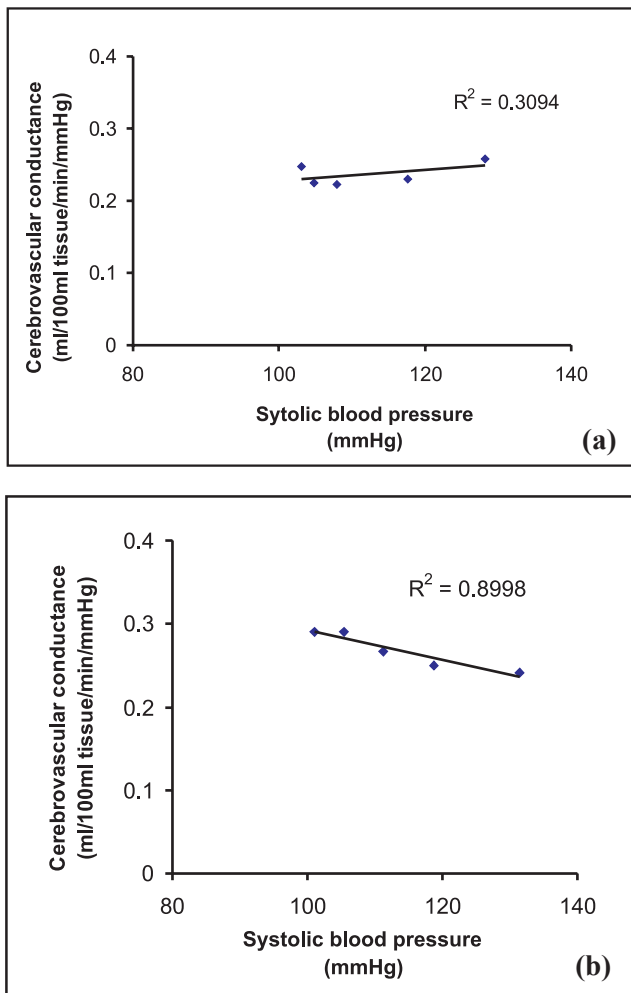
Fig. Correlation between cerebrovascular conductance and systolic blood pressure during HUT in symptomatic **(a)** and asymptomatic **(b)** patient.

Table IV. Average cerebral vascular conductance (ml/100 ml tissue/min/mmHg) at different time points in symptomatic and asymptomatic patients

Time Points (min)	Symptomatic (n=7)	Asymptomatic (n=8)
Baseline	0.26 ± 0.06	0.24 ± 0.09
0.5	0.23 ± 0.06	0.25 ± 0.10
1	0.22 ± 0.07	0.26 ± 0.11
3	0.25 ± 0.08	0.29 ± 0.14*
5	0.23 ± 0.06	0.29 ± 0.12*

*$P<0.05$, as compared to baseline (paired 't' test); Data presented as mean ± SD

Table V. Maximum changes in the cerebral blood flow (CBF), systolic blood pressure (SBP) during HUT in patients

Parameters	Symptomatic (n=7)	Asymptomatic (n=8)
Max fall in CBF (ml/100 ml tissue/min)	9.71* (8.72-14.23)	4.35 (3.15-7.13)
Max fall in SBP (mmHg)	29.14 ± 10.94	29.5 ± 6.39
Percentage fall in CBF	38.8* (25.7-41.7)	18.7 (9.95-23.09)
ΔCBF/ΔSBP (ml/100 ml tissue/min/mmHg)	0.32* (0.30-0.64)	0.14 (0.09-0.24)

*$P<0.05$ compared to asymptomatic patients (Mann-Whitney U test) Data presented as median (interquartile range)

blood pressure for each patient (Table V). The fall in systolic blood pressure was similar in symptomatic and asymptomatic but the fall in the cerebral blood flow per unit fall in systolic pressure was significantly higher in the symptomatic patients.

Discussion

The supine systolic blood pressure and resting cardiac index of the patients was significantly higher than the controls. The similar findings have been reported in the literature as supine hypertension in the patients of the orthostatic hypotension[2,18-20]. Three patients had supine blood pressure higher than 140/90 mmHg. A higher supine systolic blood pressure is thought to be due to loss of buffering mechanisms of the baroreflex system[19]. The higher cardiac index in the orthostatic pressure could be a physiological compensatory mechanism to ensure maintenance of blood pressure and cerebral perfusion during orthostasis in patients of orthostatic hypotension[9].

The sympathetic and parasympathetic reactivity was lower in the patients of orthostatic hypotension as compared to the controls. All the tests of parasympathetic reactivity and sympathetic reactivity showed lower values in the patient group. Ejaz *et al*[21] have reported 99 per cent prevalence of autonomic abnormality in 100 consecutive patients of orthostatic hypotension. Thus, it appears that autonomic function abnormality is common contributor to the pathophysiology of orthostatic hypotension[21].

The application of orthostatic stress results in decrease in the systolic as well as diastolic blood pressure in patient group[22,23]. We found that decrease in systolic pressure occurs maximally at 3rd min of head up tilt in patients. Our study substantiates the view that 3 min are sufficient for diagnosis of orthostatic hypotension[2,24]. In control subjects, during HUT the diastolic blood pressure was significantly higher than

the baseline. This is due to vasoconstriction of peripheral blood vessels initiated as part of baroreflex response to orthostatic stress in control subjects. The diastolic blood pressure in patients of orthostatic hypotension falls because of inadequate vasoconstriction.

In patients, the cerebral blood flow remained low for the duration of HUT. The percentage fall in the cerebral blood flow was 28.75 per cent in patients and 5 per cent in controls. The studies using Doppler method have reported a fall of cerebral blood by 22, 46, 36 and 39 per cent in the patients of orthostatic hypotension[6,9,20,25]. The fall in the cerebral blood flow by Doppler method in healthy controls during orthostasis have been reported to be 9, 19 and 4.83 per cent[8,9,24].

Cerebrovascular conductance did not change in the symptomatic patients while it was significantly higher in the asymptomatic patients as compared to baseline at 3rd and 5th min of HUT. The increase in cerebrovascular conductance during HUT maintains the cerebral blood flow despite fall in blood pressure and is indicative of autoregulation. Such increase was not seen in the symptomatic patients.

The small number of patients (7 symptomatic and 8 asymptomatic) limits the statistical validity of the study. A study with larger number of subjects will have to be done to validate the results of this study. Also, other factors known to affect cerebral blood flow such as partial pressure of carbon dioxide in blood, sympathetic muscle nerve activity, *etc*. were not measured simultaneously during the HUT in this study.

In conclusion, this study showed that autonomic dysfunction was common in the patients of orthostatic hypotension irrespective of presence or absence of symptom. The patients had higher supine blood pressure and cardiac index. The asymptomatic patients showed increase in cerebrovascular conductance during HUT while in symptomatic patients, the conductance did not change during HUT. Thus, dysfunction in cerebral autoregulation appears to be an essential contributor for the development of symptoms over and above cardiovascular autonomic deficits in patients of orthostatic hypotension.

Acknowledgment

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