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RESEARCH ARTICLE

ORTHOSTATIC HYPOTENSION: CARDIOVASCULAR AUTONOMIC PROFILE IN THE SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

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ABSTRACT

Purpose: Autonomic dysfunction is an important cause of orthostatic hypotension. Patients of orthostatic hypotension may or may not be symptomatic. The study was conducted to evaluate cardiovascular autonomic status in symptomatic and asymptomatic patients of orthostatic hypotension.

Methods: The study was conducted in 15 patients of orthostatic hypotension and 15 age matched subjects. On the basis of history the patients were grouped control groups symptomatic and asymptomatic. 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.

Results: The heart rate variability and measures of autonomic reactivity were lower in the patients with orthostatic hypotension as compared to control. However, they were similar between the symptomatic and asymptomatic groups. The parasympathetic component of the heart rate variability and reactivity test was more affected in patients. The fall in the blood pressure on orthostasis was similar between the symptomatic and asymptomatic patients.

Conclusion: 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 may play a crucial in development of symptoms.

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INTRODUCTION

Orthostatic 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'' (Harms *et al.,* 2000). Symptoms like dizziness, light-headedness', weakness, blurred vision, impaired concentration, and loss of consciousness are seen in patients when the cerebral perfusion is compromised on standing (Bradley *et al.,* 2003; Goldstein *et al.,* 2003). The etiology of orthostatic hypotension includes neural and non-neural factors (Task force, 1996). Even though dysfunctions of autonomic system are included as an important cause of orthostatic hypotension only a few studies have objectively documented it. Autonomic abnormality in 19 of 42 patients using objectives tests of autonomic function like Valsalva manueuvre, Deep breathing test and Cold pressor test has been reported (Lahrmann *et al.,* 2006). More recently, autonomic dysfunction was reported in 99 out of 100 consecutive patients irrespective of aetiology or comorbid conditions (Mathias and Bannister, 1999).

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Heart Rate Variability (HRV) is an important indicator of autonomic control of the heart (Ward and Kenny, 1996). Low heart rate variability has been reported in time domain as well as frequency domain in patients of orthostatic hypotension with known dysautonomia (Ejaz *et al.,* 2004). Low sympathetic component has been shown in patients of Parkinson's disease with orthostatic hypotension (Novak *et al.,* 1998). 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 (Gupta and Lipsitz, 2007; Hilz *et al.,* 2002). The patients were sub-grouped on the basis of presence of symptoms into symptomatic and asymptomatic group and compared for cardiovascular autonomic functions.

MATERIALS AND METHODS

Subjects: The study was conducted in the Autonomic function laboratory of the Department of Physiology, All India Institute

of Medical Sciences, New Delhi 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 70° head up tilt (Barbic *et al.,* 2007). 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 resting 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 electrocardiographic (ECG) recordings and respiration was monitored with stethographic tracings recorded on the polygraph (Recorders and Medicare Systems, Ambala, India). 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 manueuvre, 30:15 ratio during head up tilt.

Protocol

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 average value of 6 cycles was computed for each subject. 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 Nevrocard software (version 6.4, Medistar, Slovenia). The R wave was detected and checked for conformity. The analysis of the detected RR waveform was carried out in time and frequency domain.

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

- **SDNN** - Standard deviation of all RR intervals. It is mathematically equal to the total power of the spectral analysis and reflects all the cyclic components responsible for the variability in the period of recording.
- **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. It is a measure of parasympathetic component of heart rate variability.
- **SDSD** - Standard deviation of differences between adjacent RR intervals. It is also a measure of parasympathetic component of the heart rate variability.

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

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 2 patients reported dizziness during lying to standing test. Out of 7 symptomatic patients, 2 were diagnosed as orthostatic hypotension without any other apparent clinical illness, 1 with

Parkinson's disease, 1 with pure autonomic failure, 1 with spinocerebellar ataxia and 2 with diabetes mellitus type II. Out of 8 asymptomatic patient, 6 were diagnosed with type II diabetes mellitus, 1 with Parkinson's disease and 1 with essential hypertension. The age, gender distribution, resting blood pressure of the patients and control subjects in supine position is shown in Table 1. The fall in systolic blood pressure during head up tilt confirmed the diagnosis of orthostatic hypotension in the patients (30.93 $\pm$ 8.71 mmHg). The supine systolic blood pressure was significantly higher in the patients as compared to the control subjects. The Table 2 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. The data was re-evaluated to categorize each subject as having abnormal or normal result for each test according to the normative values published in the literature (*vide method*). Table 3 shows number of patients and controls that had abnormal result for each test. The abnormalities in the autonomic reactivity tests were significantly higher in the patients as compared to controls except in 30:15 ratio. To investigate the relationship between status of autonomic dysfunction and symptoms, the patients were sub-grouped as symptomatic and asymptomatic.

Table 1. Age, gender distribution and supine blood pressure in patients and control subjects (mean ± SD)

Parameter	Patients (n=15)	Controls (n=15)	p value
Age (years)	41.80 ± 12.86	41.74 ± 11.89	0.99
Male, female(n)	5, 10	5, 10	1.00
Systolic blood pressure (mm Hg)	130.00 ± 15.82	118.93 ± 13.26	0.047
Diastolic blood pressure (mm Hg)	82.53 ± 10.26	77.60 ± 8.39	0.154

Table 2. 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

Parasympathetic reactivity was estimated by 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. Sympathetic reactivity was measured by ΔDBP = rise in diastolic pressure during HGT = hand grip test and CPT = cold pressor test. Data is presented as median (interquartile range). Mann-Whitney U test was applied.

Table 3. Number of patients and control subject with abnormal result for each test of autonomic reactivity

Test	Number of Patients with abnormal test (out of 15)	Number of controls with abnormal test (out of 15)	p value
LST	15	0	0.001
HGT	6	0	0.017
CPT	7	1	0.035
E: I	13	1	0.001
VR	7	1	0.033
30:15	7	2	0.109

CPT = cold pressor test, ΔDBP = rise in diastolic blood pressure, E:I = Expiration to inspiration ratio, HGT = hand grip test, LST = lying to standing test, VR = Valsalva ratio, Fischer's exact test was applied for compute p value.

Table 4. 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. Parasympathetic reactivity was estimated by 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. Sympathetic reactivity was measured by ΔSBP = fall in systolic blood pressure during lying to standing test, ΔDBP = rise in diastolic pressure during HGT = hand grip test and CPT = cold pressor test.

Table 5. Number of symptomatic and asymptomatic patients with abnormal result for each test of autonomic reactivity

Test	Number of symptomatic with abnormal test (out of 7)	Number of asymptomatic with abnormal test (out of 8)	p value
LST	7	8	1.00
HGT	5	2	0.13
CPT	4	3	0.60
E: I	6	7	1.00
VR	3	4	1.00
30:15	2	5	0.30

CPT = cold pressor test, E:I = Expiration to inspiration ratio, HGT = hand grip test, LST = Lying to standing test, VR = Valsalva ratio. Fischer's exact test was applied for compute p value.

Table 6. 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

Heart rate variability was computed from 5 minute ECG was recorded in resting state. pNN50 = percentage of successive RR interval with difference more than 50 ms, SDNN = standard deviation of all RR intervals, SDSD = standard deviation of differences in successive RR intervals. LF = low frequency band (0.05 – 0.15 Hz) , LF/HF = ratio of power in low frequency and high frequency. HF = high frequency band (0.15 – 0.40 Hz), Data is presented as median (interquartile range). Mann-Whitney U test was applied. (n.u. = normalized units, ab = absolute).

Table 7. Heart rate variability in symptomatic and asymptomatic patients

Parameters	Symptomatic (7)	Asymptomatic (8)	p value
Time domain			
SDNN (ms)	33.85 (2.00 – 36.56)	11.51 (8.6 – 16.09)	0.08
pNN50 (%)	2.78 (0.00 – 7.06)	0.00 (0.00 – 0.20)	0.13
SDSD (ms)	29.9 (14.3 – 37.64)	9.94 (6.20 – 20.60)	0.049
Frequency domain			
LF/HF (n.u.)	1.32 (0.33 – 2.55)	0.78 (0.43 – 1.96)	1.00
LF power (n.u.)	52.36 (23.70 – 64.40)	31.04 (24.00 – 41.50)	0.64
HF power (n.u.)	39.61 (23.71 – 68.01)	47.40 (16.98 – 59.90)	0.64
Total power (ab)	1026.32 (293.3 – 3141.06)	169 (88.51 – 280.64)	0.03

Heart rate variability was computed from 5 minute ECG was recorded in resting state. pNN50 = percentage of successive RR interval with difference more than 50 ms, SDNN = standard deviation of all RR intervals, SDSD = standard deviation of differences in successive RR intervals. LF = low frequency band (0.05 – 0.15 Hz) , LF/HF = ratio of power in low frequency and high frequency. HF = high frequency band (0.15 – 0.40 Hz), Data is presented as median (interquartile range). Mann-Whitney U test was applied. (n.u. = normalized units, ab = absolute).

The results of the autonomic tests in symptomatic and asymptomatic are shown as quantitative values in table 4 and as categorical value in Table 5. The symptomatic and asymptomatic group did not differ for the results of autonomic reactivity.

Heart rate variability: Table 6 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 (Table 7) 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 or absence of symptoms in the patients. The supine systolic blood pressure was higher in the patients. Similar observations have been reported earlier (Hohnloser *et al.,* 1998; Robertson, 2008; Ejaz *et al.,* 2007). 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 (Robertson, 2008). 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.,* 2008. (Lahrmann *et al.,* 2006; Mathias and Bannister, 2009) More importantly we find that parasympathetic reactivity is more commonly lost as compared to sympathetic reactivity. 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 was 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 patients. 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 (Guo *et al.,* 2006). 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, (Gehrking *et al.,* 2005). 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 (Ejaz *et al.,* 2007). Pooling of blood in normal subjects can lead to downward shift in the autoregulatory range of cerebral perfusion (Gehrking *et al.,* 2005). On this basis, we postulate that dysfunction of cerebral autoregulation or downward shift in the autoregulatory set-point is a major contributor to the development of symptoms in patients of orthostatic hypotension. 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. Small sample size of the sub-group and heterogeneous medical condition associated with orthostatic hypotension does limit the conclusion of the study. These finding needs to be confirmed with higher number of subjects in the symptomatic and asymptomatic group with homogenous background medical condition along with estimation of the cerebral autoregulation.

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REFERENCES

Barbic, F., Perego, F., Canesi, M., Gianni, M., Biagiotti, S., Costantino, G. et al. 2007. Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. *Hypertension*, 49:21-2.

Bradley, J. G., Davis, K. A. 2003. Orthostatic hypotension. *Am Fam Physician*, 68:2393-8.

Ejaz, A. A., Haley, W. E., Wasiluk, A., Meschia, J. F., Fitzpatrick, P. M. 2004. Characteristics of 100 consecutive patients presenting with orthostatic hypotension. *Mayo Clin Proc*., 79:890-4.

Ejaz, A. A., Kazory, A., Heinig, M. E. 2007. 24-hour blood pressure monitoring in the evaluation of supine hypertension and orthostatic hypotension. *J Clin Hypertens., 9:952-55.*

Gehrking, J. A., Hines, S. M., Benrud-Larson, L. M., Opher-Gehrking, T. L., Low, P. A. 2005. What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension? *Clin Auton Res*., 15:71-5.

Goldstein, D. S., Pechnik, S., Holmes, C., Eldadah, B., Sharabi, Y. 2003. Association between supine hypertension and orthostatic hypotension in autonomic failure*. Journal of American heart association*, 42: 136-42.

Guo, H., Tierney, N., Schaller, F., Raven, P. B., Smith, S. A., Shi, X. 2006. Cerebral autoregulation is preserved during orthostatic stress superimposed with orthostatic hypotension. *J Appl Physiol*., 100: 1785- 92.

Gupta, V., Lipsitz, L. A. 2007. Orthostatic hypotension in elderly: diagnosis and treatment. *Am J Med*., 120: 841–7.

Harms, M., Colier, W., Wieling, W., Lenders, J., Secher, N., Lieshout, J. 2000. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke*, 3:1608-14.

Hilz, M. J., Axelrod, F. B., Haertl, U., Brown, C. M., Stemper, B. 2002. Transcranial Doppler sonography during head up tilt suggests preserved central sympathetic activation in familial dysautonomia. *J Neurol Neurosurg. Psychiatry*, 72: 657-60.

Hohnloser, S. H., Klinenheben, T. 1998. Basic autonomic tests. In : Marek Malik, editor. Clinical guide to cardiac autonomic test. *Kluwer Academic Publisher London*, pp.51–65.

Lahrmann, H., Cortelli, P., Hilz, M., Mathias, C. J., Struhal, W., Tassinari, M. 2006. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurol.,* 13:930-6.

Mathias, C. J., Bannister, R. 1999. 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, pp.169 – 95.

Novak, V., Novak, P., Spies, J. M., Low, P. A. 1998. Autoregulation of cerebral blood flow in orthostatic hypotension. *American heart association*, 29: 104-11.

Robertson, D. 2008. The pathophysiology and diagnosis of orthostatic hypotension. *Clin Auton Res*., 18: 2-7

Shi, X., Wray, D. W., Formes, K. J., Wang, H. W., Hayes, P. M., O-Yurvati, A. H. et al. 2000. Orthostatic hypotension in aging humans. *Am J Physiol*., 279: 1548 - 54.

Task force, 1996. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*, 93:1043-65.

Ward, C., Kenny, R. A. 1996. Reproducibility of orthostatic hypotension in symptomatic elderly. *American journal of medicine*, 100:418-22.

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