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Protocol paper

When should orthostatic blood pressure changes be evaluated in elderly: 1st, 3rd or 5th minute?

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ABSTRACT

Detection of orthostatic hypotension (OH) is very important in geriatric practice, since OH is associated with mortality, ischemic stroke, falls, cognitive failure and depression. It was aimed to determine the most appropriate time for measuring blood pressure in transition from supine to upright position in order to diagnose OH in elderly. Comprehensive geriatric assessment (CGA) including Head up Tilt Table (HUT) test was performed in 407 geriatric patients. Orthostatic changes were assessed separately for the 1st, 3rd and 5th minutes (HUT_1, HUT_3 and HUT_5, respectively) taking the data in supine position as the basis. The mean age, recurrent falls, presence of dementia and Parkinson's disease, number of drugs, alpha-blocker and anti-dementia drug use, and fasting blood glucose levels were significantly higher in the patients with versus without OH; whereas, albumin and 25-hydroxy vitamin D levels were significantly lower ($p < 0.05$). However, different from HUT_3 and HUT_5, Charlson Comorbidity Index and the prevalence of diabetes mellitus were higher, the use of antidiabetics, antipsychotics, benzodiazepine, opioid and levodopa were more common ($p < 0.05$). Statistical significance of the number of drugs and fasting blood glucose level was prominent in HUT_1 as compared to HUT_3 ($p < 0.01$, $p < 0.05$). Comparison of the patients that had OH only in HUT_1, HUT_3or HUT_5 revealed no difference in terms of CGA parameters. These results suggests that orthostatic blood pressure changes determined at the 1st minute might be more important for geriatric practice. Moreover, 1st minute measurement might be more convenient in the elderly as it requires shorter time in practice.

1. Introduction

The prevalence of orthostatic hypotension (OH) increases with age and it is 10–30% in elderly (Low, 2008). Deficiency in arterial baroreflex sensitivity and venomotor control along with aging, as well as cardiac hypertrophy, decrease in renin-angiotensin aldosterone level and the sensitivity to these hormones make the management of postural blood pressure difficult (Low & Tomalia, 2015; Low, 2008; Okada et al., 2012). Besides, Parkinson's disease (PD), diabetes mellitus (DM), dehydration and malnutrition, which are common comorbidities in elderly patients, and accordingly frequent use of antihypertensive drugs, levodopa, antidepressants and benzodiazepines might enhance tendency toward OH (Low & Tomalia, 2015; Press, Punchik, & Freud, 2015). In addition to typical symptoms such as dizziness, blackout, temporary loss of conscious, weakness, nausea and drowsiness, the patients may also present with atypical symptoms such as falls and head, neck and low back pain. Asymptomatic OH, in fact, is more common in older adults than considered by the clinicians; 1/3 of the patients have OH although they have no complaint (Arbogast, Alshekhlee, Hussain, McNeeley, & Chelimsky, 2009). Detection of OH in elderly is of great importance; because, numerous studies have demonstrated association of OH with mortality, ischemic stroke, falls, cognitive failure and depression (Chou et al., 2015; Gangavati et al., 2011; Jodaitis et al., 2015). For these reasons, evaluation of orthostatic blood pressure changes (OBPC) should necessarily be a part of the comprehensive geriatric assessment (CGA).

According to the consensus statement on the definition of orthostatic hypotension published in 1996, the diagnosis of OH is made in the event of at least 20 mmHg decrease in systolic blood pressure (SBP) and/or at least 10 mmHg decrease in diastolic blood pressure (DBP) within the first 3 min of standing up (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996). Although

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measurements at the 1st and 3rd minutes of standing are recommended for the diagnosis of OH, there is yet no consensus on the optimum time of measurement for diagnosis (Campos et al., 2015; Maurer, Rivadeneira, & Bloomfield, 1998; Yasuharu et al., 2005). Delayed OH is another concept relevant to this subject and is defined as OH that develops after the 3rd minute; however, data about the prevalence and importance of this situation in elderly is limited (Podoleanu et al., 2009).

The present study aimed to determine the optimum time for clinical significance of blood pressure measurement in transition from supine to upright position while evaluating OBPC in elderly.

2. Materials and methods

2.1. Study design

A total of 407 elderly patients, who admitted to the geriatric clinic in a university hospital between January 2014 and August 2015, were included in this prospective and cross-sectional observational study. CGA including Head up Tilt Table (HUT) was performed in those geriatric patients after obtaining their informed written consents.

2.2. Inclusion criteria

The patients who were over the age of 65 years, presented to our center for any reason, and had none of the exclusion criteria.

2.3. Exclusion criteria

Patients with severe anemia (hemoglobin $<$10 g/dL), critical mitral and/or aortic valve stenosis, acute or chronic renal insufficiency, decompensated cardiac and/or hepatic insufficiency, severe carotid artery stenosis and/or coronary artery stenosis, history of cerebrovascular accident, myocardial infarction or lower extremity fracture in the last week, hypotensive shock, bradycardia or tachycardia during examination, dehydration, electrolyte imbalance, acute hemorrhage, severe metabolic acidosis, sepsis, and similar severe comorbid conditions, all of which are the contraindications for Head up Tilt Table test (HUT), were excluded (Moya et al., 2009).

2.4. Patient characteristics

Demographic data (age, gender, education status) of the patients, history of falls (according to the information obtained from the patient or patient's relatives, presence of more than one falls not associated with seizure or acute stroke in the last year) and presence of postural symptoms such as dizziness, blackout, nausea, sweating and imbalance in upright position were asked and recorded. Personal history of chronic disease (hypertension, DM, coronary artery disease, congestive heart failure, cerebrovascular disease, hyperlipidemia, peripheral vascular disease, depression, PD, and dementia), drugs they have been using, and the number of drugs were questioned in detail. In addition, comorbid conditions of the patients were assessed using Charlson Comorbidity Index (CCI).The patients underwent CGA including Mini-Mental State Examination (MMSE), Cognitive State Test (COST) (Babacan-Yildiz et al., 2013), Yesavage's geriatric depression scale (GDS), and Tinetti Performance-Oriented Mobility Assessment (POMA), Barthel activities of daily living index (ADL), Lawton-Brody instrumental activities of daily living (IADL), and Mini Nutritional assessment Short form (MNA-SF).

2.5. Laboratory findings

Certain laboratory tests were done to assess the biochemical, metabolic and nutritional status of the patients. Thus, laboratory recordings were obtained for complete blood count, kidney and liver functions, cholesterol levels, thyroid-stimulating hormone (TSH), HbA1c, vitamin D, vitamin B12, and folic acid levels. All of these biochemical tests were carried out on Diagnostic Modular Systems autoanalyzer (Roche E170 and P-800). Serum 25-Hidroksi-Vitamin D [25(OH)D] was measured by radioimmunoassay.

HUT Test was performed for the diagnosis of OH. The test was performed in the morning after the patients received their daily medications and attention was paid for the patients not smoke, intake caffeine, or exercise within 30 min prior to the test. HUT was performed by tilt Table (Gemesan® Tilt TableG-71, Turkey). Monitoring over the course of HUT was performed by Biolight® BIOM69 (Australia) with reusable adult arm cuff. After allowing the patients to have a rest in a silent room with temperature of 20–24 °C for at least 10 min in supine position, the tilt Table was rapidly and fluently raised up to an angle of 60–80°. The patients were monitored via blood pressure, mean arterial blood pressure, heart rate, electrocardiogram (ECG), and pulse oximeter over the course of HUT (Parry et al., 2009). The data of monitoring at the 1st, 3rd and 5th minutes (HUT_1, HUT_3 and HUT_5, respectively) were recorded, and the patients were questioned whether they had postural symptoms such as dizziness, blackout and nausea.

The diagnosis of OH was made in the event of 20 mmHg and higher decrease in systolic pressure and/or 10 mmHg and higher decrease in diastolic pressure during transition from supine position to at least 60° head-up position during HUT (Parry et al., 2009; The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996). According to this definition, OBPC at the 1st, 3rd and 5th minutes were evaluated taking the data of supine position as the basis.

2.6. Postural tachycardia syndrome

Postural tachycardia syndrome was defined as an increase in heart rate (>120 beat/min or an increase more than 30 beat/min as compared to baseline values) without OH during HUT test (Low, Sandroni, Joyner, & Shen, 2009).

2.7. Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation and evaluated by Kolmogorov-Smirnov test for normal distribution. Normally distributed continuous variables with normal distribution were analyzed by paired sample *t*-test. In case of non-normal distribution, continuous variables were evaluated by Mann-Whitney *U* test. Differences between categorical variables were evaluated by Chi-square and Fisher's exact Chi-square tests. The Cochran's Q test was used to compare proportions within groups. Comparison of the patients that had OH only in HUT_1, HUT_3 or HUT_5 were assessed by Kruskal-Wallis Test. A probability <0.05 was considered significant. All statistical analyses were done using SPSS 15.0 (SPSS Inc.) package program. Adequate sample size was calculated (298 patients for%95 confidence interval).

2.8. Ethics

The study was conducted in conformity with the Declaration of Helsinki and was approved by the ethics committee of the School of Medicine, Dokuz Eylul University in Izmir, Turkey (2013/23-08).

3. Results

The prevalence of OH during HUT_1, HUT_3 and HUT_5 was 21.86%, 21.37% and 19.90%, respectively. The differences between the groups with and without OH during HUT_3 are demonstrated in Table 1. It was determined that all parameters significant for OH during HUT_3 were significant also during HUT_1 and HUT_5. In addition, CCI and prevalence of DM was higher, the use of antidiabetic, antipsychotic, opioid, and levodopa was more common, but hemoglobin concentration was lower in those with OH during HUT_1 ($p < 0.05$). Statistical significance of the number of drugs used and fasting blood glucose level was much higher for HUT_1 than for HUT_3 ($p < 0.01$ and $p < 0.05$, respectively) (Table 1).

Table 1
Patient characteristics according to 3rd minute Orthostatic Blood Pressure Change.

	OH (−) (n:317)	OH (+) (n:90)	P value
Age	74.14 ± 8.63	78.73 ± 7.80	0.000
Sex (female/male)	204/113	52/38	0.254
Education	4.53 ± 3.69	4.40 ± 4.14	0.401
Recurrent falls %	24.6	45.6	0.000
Postural Symptoms	48.9	45.6	0.576
CCI	1.19 ± 1.31	1.40 ± 1.44	0.197
Comorbidities %			
Hypertension	67.2	71.1	0.482
*Diabetes Mellitus	25.2	30.0	0.365
Coronary Artery Disease	19.9	14.4	0.243
Hyperlipidemia	17.7	16.7	0.826
Chronic Heart Failure	7.6	8.9	0.682
COPD	10.4	4.4	0.082
CVD	6.0	5.6	0.876
PVD	2.2	2.1	0.950
Hypothyroidism	13.2	11.1	0.592
Depression	40.4	31.1	0.111
Dementia	21.5	37.8	0.002
Parkinson Disease	3.7	8.8	0.022
**Number of drugs used	4.77 ± 2.98	5.65 ± 3.04	0.021
RAASB	48.3	45.6	0.650
Diüretics	34.1	32.2	0.743
Calcium channel blockers	18.9	23.3	0.356
Beta blockers	24.9	31.1	0.239
Alpha blockers	7.3	14.4	0.034
Nitrates	5.0	3.3	0.496
Antihyperlipidemic agents	16.7	15.6	0.793
*Antidiabetic agents	23.7	23.3	0.949
Levothyroxine	11.4	10.0	0.717
PPI	19.9	25.6	0.244
SSRI	30.3	23.3	0.199
SNRI	4.7	5.6	0.750
Trazodone	7.9	6.7	0.700
Antidementia drugs	16.7	34.4	0.001
*Antipsychotics	6.0	7.8	0.541
*Benzodiazepines	7.6	4.4	0.301
*Opioids	3.5	6.7	0.181
*Levodopa	2.2	4.4	0.248
Antimuscarinic drugs for OAB	7.6	5.6	0.512
NSAID	2.5	4.4	0.262
Laboratory Data			
*Hemoglobin (g/L)	12.97 ± 1.38	12.82 ± 1.55	0.388
*Fasting Blood Glucose (mg/dl)	106.13 ± 35.43	111.03 ± 38	0.028
Albumin (g/l)	4.12 ± 0.31	3.90 ± 0.37	0.000
LDL-C (mg/dL)	131.01 ± 37.46	127.06 ± 39.64	0.412
HDL-C (mg/dL)	54.92 ± 14.14	53.77 ± 14.31	0.523
TSH (uIU/mL)	1.50 ± 0.97	1.55 ± 1.12	0.741
HbA1c	6.96 ± 1.30	6.73 ± 1.31	0.455
Folic acid (ng/mL)	8.98 ± 4.48	8.84 ± 4.87	0.549
Vitamin B12 (pmol/L)	432.36 ± 219.60	483.56 ± 239.54	0.088
25(OH)D (ng/ml)	19.73 ± 11.35	16.52 ± 12.31	0.002

CCI: Charlson Comorbidity Index, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cerebrovascular Disease, HDL-C: High- density lipoproteins cholesterol, LDL-C: Low-density lipoproteins cholesterol, NSAID: Nonsteroidal anti-inflammatory drug, OAB: Overactive bladder, OH: Orthostatic Hypotension, PPI: Proton pump inhibitor, PVD: Peripheral vascular Disease, RAASB: Renin-angiotensin-aldosterone system blocker, SNRI: Serotonin–norepinephrine reuptake inhibitor, SSRI: Selective serotonin receptor inhibitor, TSH: Thyroid − stimulating hormone.

* $p < 0.05$;Statistical significance at 1st minute Orthostatic Blood Pressure Changes.

** $p < 0.01$; Statistical significance at 1st minute Orthostatic Blood Pressure Changes.

Characteristics of the patients during HUT_1, HUT_3 and HUT_5 are demonstrated in Table 2. Accordingly, there was no difference between the prevalence of OH, systolic OH (SOH), diastolic OH (DOH), POTS and MABP-change ($p < 0.05$).

There were 29 subjects with OH only during HUT_1, 18 subjects with OH only during HUT_3 and 12 subjects with OH only during HUT_5. Comparison of these three groups according to CGA measurements revealed no differences in terms of age, cognition, mood, nutritional status, activities of daily life and balance function ($p > 0.05$) (Table 3).

The percentage of asymptomatic patients with OH was 86.2% during HUT_1, 86.7% during HUT_3 and 84% during HUT_5.

4. Discussion

The present study evaluated OBPC in elderly patients at the 1st, 3rd and 5th minutes after standing; it was determined that the 1st minute measurement might be adequate and effective to assess OH in elderly.

OH is a prevalent geriatric syndrome but may be overlooked despite numerous complications such as mortality, ischemic stroke, falls, cognitive deficit, depression, and sleep disorders (Chou et al., 2015; Gangavati et al., 2011; Jodaitis et al., 2015). In the literature, the prevalence of disease and related findings show variation due to the use of different definitions and methods. Whilst some studies underline that OBPC should be assessed just after standing up; otherwise, the changes would be missed during long waiting period (Belmin et al., 2000; Gupta & Lipsitz, 2007; Lance et al., 2000), some authors defend that at least 10 min of up-right position is required to determine such changes (Gurevich et al., 2014; Podoleanu et al., 2009). The fact that some studies have used active standing test but some others have used HUT testing much more enhances the confusion. Even if it is considered that HUT is not relevant to daily practice since it does not allow for active muscle pump reflex to prevent venous pooling; it should kept in mind that HUT is most helpful in evaluating measures of OH (Lamarre-Cliche & Cusson, 2001). Specific diagnostic criteria in older adult for OH have not been identified yet despite changing compensatory mechanisms, multiple comorbid diseases and multiple drugs use in elderly. Moreover, diagnosis of OH in clinical practice is time-consuming, which poses greater problem in the evaluation of elderly patients. Therefore, the present study aimed to determine the most appropriate time for the measurement of orthostatic changes in blood pressure in elderly.

In the present study, the prevalence of OH in elderly was 21.86% and 21.37% at the 1st and 3rd minutes, respectively and was similar

Table 2
Comparison of the patients' characteristics between the groups with OH at 1th, 3rd, 5th minutes.

	1st minute	3rd minute	5th minute	P value
OH (n)	89	87	81	0.542
SOH (n)	70	72	70	0.947
DOH(n)	36	34	31	0.581
POTS (n)	5	4	8	0.115
MABP*	2.54 ± 13.62	1.98 ± 13.81	2.67 ± 13.72	0.128

DOH: Diastolic Orthostatic Hypotension, MABP: Mean Arterial Blood Pressure, OH: Orthostatic Hypotension, POTS: Postural orthostatic tachycardia syndrome, SOH: Systolic Orthostatic Hypotension.

* Mean Changes between at the up-right position time and at the supine position.

Table 3
Comparison of the patients between the groups with OH only at 1th, 3rd, 5th minutes.

	1th minute (n:29)	3th minute (n:18)	5th minute (n:12)	p value
Age	77.20 ± 6.95	79.16 ± 4.74	74.91 ± 6.94	0.193
MMSE	21.41 ± 6.25	21.44 ± 6.32	22.85 ± 6.71	0.081
COST	21.22 ± 6.72	18.14 ± 7.64	24.00 ± 4.54	0.301
YGDS	4.30 ± 3.37	4.08 ± 3.75	1.75 ± 3.05	0.091
MNA	10.92 ± 2.21	10.00 ± 3.44	11.80 ± 1.81	0.242
BADL	85.53 ± 17.50	79.68 ± 21.10	95.40 ± 5.33	0.088
IADL	8.53 ± 5.48	8.12 ± 5.36	11.50 ± 4.62	0.242
POMA	20.43 ± 7.46	20.19 ± 7.25	20.50 ± 6.19	0.698
CCI	1.79 ± 1.29	1.47 ± 1.23	1.50 ± 0.84	0.627

BADL: Basic activity of daily living (0 [worst]-100 [best]); CCI: CharlsonComorbidity Index COST: Cognitive State Test(0 [worst]-30 [best]); IADL: Instrumental activity of daily living (0 [worst]-17 [best]); MMSE: Mini-Mental State Examination (0 [worst]-30 [best]); MNA: Mini Nutritional Assessment (0 [worst]-14 [best]); POMA:Tinetti performance oriented mobility assessment (0 [worst]-26 [best]); YGDS: Yesavage Geriatric Depression Score (15 [worst]-0 [best]).

to the results of earlier studies (Gupta & Lipsitz, 2007). The prevalence of delayed OH, the clinical significance of which is yet unclear but has been reported by Gibbons and Freeman (2015) to be associated with mortality and synucleinopathy, was 19.9% in the present study (Gibbons & Freeman, 2015). Tanya Gurevich et al. (2014) evaluated delayed OH in 270 patients for 40 min using HUT and determined that decrement in orthostatic blood pressure increased cumulatively over the course of testing period but, different from the young people, elderly people required much shorter time for the development of OH (Gurevich et al., 2014). In another study, the patients were evaluated for OH in ≤3 min, 3–10 min and >10 min; similar to the previous study, it was demonstrated that the mean age was the highest in the ≤3-minute group and that the number of patients increased as the time was extended (Gibbons & Freeman, 2006). In addition to these studies, Yasuharu et al. (2005) one of the limited studies conducted on this subject in elderly patients, have taken only 20 mmHg decrease in systolic pressure as the criterion and evaluated 237 patients at the 1st and 3rd minutes by active standing test; they reported that the 1st-minute measurement may be adequate for postural hemodynamic changes (Yasuharu et al., 2005). In the light of these outcomes, it is clear that keeping the patient in upright position for a long time (>10 min) would not provide additional benefit in diagnosing OH in the elderly. In the present study, patients with OH were mostly identified at the 1st minute. The number of patients that developed OH at the 3rd or 5th minute was quite less and 4% and 2%, respectively. Moreover, the fact that no differences among the patients that developed OH at three time points according to cognitive status, depressive mood, nutritional status, activities of daily living and gait-balance functions supports that 1st-minute measurement might be adequate in elderly patient, in geriatric practice.

On the other hand, it has been determined that OH is associated with recurrent falls and that the risk factors for OH include age, polypharmacy, alpha blocker and anti-dementia drugs use, hypoalbuminemia, hyperglycemia, dementia, and vitamin D deficit (Gupta & Lipsitz, 2007). These findings were similar with the results of earlier studies in the literature (Monsuez, Beddok, Mahiou, Ngaleu, & Belbachir, 2012; Soysal, Yay, & Isik, 2014). However, it was found that DM, anemia and presence of multiple comorbidities, which are well known to cause OH, as well as the use of antipsychotics, benzodiazepine, opioid and levodopa, are associated only with OH at the 1st minute (Kanjwal, George, Figueredo, & Grubb, 2015; Pepersack et al., 2013). Besides, the relation between polypharmacy, high fasting blood glucose and OH was more significant at the 1st minute as compared to the other time points (Kamaruzzaman, Watt, Carson, & Ebrahim, 2010; Press et al., 2015; Takahashi & Miyai, 2015). Based on these outcomes, it can be speculated that clinical reflection of 1stminute OBPC in elderly is as significant as at least the 3rdminute measurement and even might be more valuable in certain situations. Moreover, the fact that the 1st minute measurement shortens duration of evaluation might help in clinical practice.

More often OH is seen in the elderly with numerous pathologies and polypharmacy, without a single cause. The elderly patients are particularly prone to develop OH because aging is associated with impairment of various compensatory mechanisms to orthostatic changes. They have decreased baroreflex sensitivity, with diminished heart rate responses and impaired α1-adrenergic vasoconstriction (Gupta & Lipsitz, 2007). There are age-related alterations in parasympathetic tone that result in less cardioacceleration during vagal withdrawal on standing (Shibao, Lipsitz, & Biaggioni, 2013). The elderly are particularly prone to dehydration, since they often have an impaired thirst sensation, and the aged kidney loses some of its ability to conserve salt and water during periods of fluid restriction or volume loss because of a reduction of renin, angiotensin, and aldosterone and an elevation in natriuretic peptides (Shibao et al., 2013). The heart is also stiff and noncompliant, resulting in impaired diastolic filling, which reduces stroke volume, particularly during the decrease in venous return that results from orthostasis (Gupta & Lipsitz, 2007; Shibao et al., 2013). All these age-related physiological changes increase the risk of OH in the elderly. Both all these physiological alterations and accompanying comorbidities, drugs and vitamin deficiency may cause OH during early standing by impairing compensatory response to orthostatic changes. Therefore, OBPC should be evaluated by measuring in 1st minute after standing up. However, future studies on this subject would enlighten this hypothesis.

Limitations of the present study include the absence of measurements at the 2nd minute and after the 5th-minute as well as the absence of physiopathological evaluation. In addition, it seems as if the exclusion of some elderly patients due to the contraindications for HUT is a limitation, it is clear that our study population reflects the most of the geriatric patients for the objective evaluation of OH. The powerful aspects of the study, however, include prospective design, adequate sample size, the use of HUT test for diagnosis, and evaluation of the relation between OH and patient-related details such as comorbidities, drugs and laboratory findings.

In conclusion, OBPC determined at the 1st minute may be of higher clinical significance to evaluate OH in elderly patients, compare to 3rd or 5th minute. First-minute measurement appears to be adequate for the diagnosis of OH in clinical practice as it takes shorter time and identifies most of the cases.

Conflicts of interest

All authors have no financial or any other kind of personal conflicts whit this paper.

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