



# Heart-Rate-Based Machine-Learning Algorithms for Screening Orthostatic Hypotension

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**Background and Purpose** Many elderly patients are unable to actively stand up by themselves and have contraindications to performing the head-up tilt test (HUTT). We aimed to develop screening algorithms for diagnosing orthostatic hypotension (OH) before performing the HUTT.

**Methods** This study recruited 663 patients with orthostatic intolerance (78 with and 585 without OH, as confirmed by the HUTT) and compared their clinical characteristics. Univariate and multivariate analyses were performed to investigate potential predictors of an OH diagnosis. Machine-learning algorithms were applied to determine whether the accuracy of OH prediction could be used for screening OH without performing the HUTT.

**Results** Differences between expiration and inspiration (E-I differences), expiration:inspiration ratios (E:I ratios), and Valsalva ratios were smaller in patients with OH than in those without OH. The univariate analysis showed that increased age and baseline systolic blood pressure (BP) as well as decreased E-I difference, E:I ratio, and Valsalva ratio were correlated with OH. In the multivariate analysis, increased baseline systolic BP and decreased Valsalva ratio were found to be independent predictors of OH. Using those variables as input features, the classification accuracies of the support vector machine, *k*-nearest neighbors, and random forest methods were 84.4%, 84.4%, and 90.6%, respectively.

**Conclusions** We have identified clinical parameters that are strongly associated with OH. Machine-learning analysis using those parameters was highly accurate in differentiating OH from non-OH patients. These parameters could be useful screening factors for OH in patients who are unable to perform the HUTT.

**Key Words** orthostatic hypotension, heart rate, Valsalva maneuver, machine learning.

## INTRODUCTION

Orthostatic hypotension (OH) is defined as a reduction of the systolic blood pressure (BP) of at least 20 mm Hg or of the diastolic BP of 10 mm Hg within 3 minutes of standing or head-up tilting from a lying or sitting position.<sup>1</sup> Because OH is a clinical sign, it can be either symptomatic or asymptomatic.<sup>1</sup> OH may occur in disorders involving the autonomic nervous system (e.g., Parkinson's disease, multiple-system atrophy, pure autonomic failure, and diabetic autonomic neuropathy) as well as in various conditions such as dehydration, sepsis, and taking drugs.<sup>2,3</sup> Since OH is associated with increased risks of falling injury, cardiovascular events, and cognitive impairment, it is implicated in unfavorable outcomes and increased mortality.<sup>4-9</sup> Considering the deleterious effects of OH, early detection and timely management are needed to promote favorable outcomes and decrease the mortality rate.

While the head-up tilt test (HUTT) has been widely used for diagnosing OH, there are many patients with suspected OH who cannot hold this position on the tilt table. In addition,

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tion, while the HUTT is safe, relative contraindications have been reported including severe left ventricular outflow obstruction, critical mitral stenosis, and severe proximal coronary artery and cerebrovascular stenosis.<sup>10</sup> In addition to the physical limitations, the time and cost burdens of performing the HUTT constrains the monitoring of treatment responses and symptom progression through repeated HUTTs.

There have been efforts to identify alternative clinical markers for diagnosing OH that can overcome the limitations of the HUTT. In our previous study, patients with OH showed the most-prolonged corrected QT interval on electrocardiography among patients with orthostatic intolerance (OI) including OH, neurocardiogenic syncope, and postural tachycardia syndrome.<sup>11</sup> This finding suggests that a corrected QT interval could be a useful marker for identifying OI.<sup>11</sup> Using near-infrared spectroscopy, monitoring the pattern of cerebral perfusion changes during the Valsalva maneuver (VM) was also found to be a useful tool for identifying patients with OI as an alternative to the HUTT.<sup>12</sup> In addition, a few studies have shown a relationship between BP responses during the VM and HUTT, implying that the VM might be a nonpostural method for supplementing the HUTT in detecting and differentiating OI.<sup>13,14</sup> Although the above-mentioned methods are valuable alternatives that can be applied to patients who are unable to perform the HUTT, those methods have the limitation that beat-to-beat BP measurements using special equipment are required to obtain reliable data. However, recent technological advances have allowed the heart rate (HR) to be monitored reliably and conveniently at home using wearable electronic devices.<sup>15</sup>

If the accuracy of an algorithm utilizing HR-based parameters acquired from nonpostural stimuli without special equipment to measure the beat-to-beat BP is high enough for differentiating OI, it might be possible to diagnose OH in a timely manner while performing the usual daily activities in real time. In this study we conducted a logistic regression analysis to identify which clinical characteristics and HR-based measurements of autonomic function tests (AFTs) could be considered clinical markers for differentiating OH from non-OH patients. In addition, we applied machine-learning algorithms to determine whether the accuracy of detecting OH using clinical variables and HR-based measurements of AFTs is sufficient for screening OH before performing the HUTT to confirm the results.

## METHODS

### Subjects

We included 719 subjects with OI who underwent composite AFTs at a university-affiliated hospital from January 2017 to

December 2017. Based on the HUTT findings, these patients with OI were categorized into OH, neurocardiogenic syncope, and postural tachycardia syndrome.<sup>1</sup> Subjects who did not show any significant changes in BP or HR during the HUTT and who did not meet the criteria for OH, neurocardiogenic syncope, and postural tachycardia syndrome served as non-OH controls. Patients who had proven causative factors for OI or conditions that prevented AFTs being completed were excluded, which comprised patients with a history of developmental abnormalities, proven cardiac arrhythmia, significant head injury, alcohol or substance abuse, or psychiatric disorders. The local ethics committee approved the study protocol (IRB No. 2016AN0075).

### AFTs

All patients were requested to not consume alcohol or coffee and to discontinue any medication that could affect autonomic function for at least 24 hours prior to each test. Tests were performed in the following sequence according to the standard electrodiagnostic laboratory environment:<sup>11,16-18</sup> 1) quantitative sudomotor axon reflex test (QSART), 2) HR response to deep breathing, 3) VM, and 4) HUTT. The Composite Autonomic Scoring Score (CASS), which is a validated measurement of the severity of autonomic dysfunction, was derived from the AFTs.<sup>19</sup>

### QSART

The QSART, which was performed with the Q-Sweat device (WR Medical Electronics, Maplewood, MN, USA), provides an index of sympathetic postganglionic sudomotor function.<sup>20</sup> The stimulus consisted of 10% iontophoresed acetylcholine applied using a constant-current generator at 2 mA for 5 minutes. Sweat volumes were recorded in the central compartment of a multicompartmental sweat cell from the following four sites: 1) the medial forearm (75% of the distance from the ulnar epicondyle to the pisiform), 2) proximal leg (5 cm distal to the fibular head laterally), 3) distal leg (5 cm proximal to the medial malleolus medially), and 4) proximal foot (over the extensor digitorum brevis muscle). The QSART result was considered abnormal if the sweat volume was lower than the age- and sex-specific reference values.<sup>21</sup>

### Deep breathing and the VM

Deep breathing is used to test cardiovascular functions. The VM can be used to evaluate sympathetic adrenergic functions based on BP responses as well as cardiovascular (parasympathetic) functions based on HR responses. Both were measured with Finometer equipment (Finapres Medical Systems, Amsterdam, Netherlands) using previously described techniques.<sup>20</sup> During deep breathing (6 breaths per minute), the HR range

in response to forced respiratory sinus arrhythmia was obtained. The difference between expiration and inspiration (E-I difference) was determined by subtracting the minimum HR during expiration from the maximum HR during inspiration for each six-breath cycle. The expiration:inspiration ratio (E:I ratio) was measured as the ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration. For the VM, subjects were asked to blow through a mouthpiece attached to a manometer and maintain a pressure of 40 mm Hg for 15 seconds while in a rested and recumbent position. After a practice run, subjects performed a series of VMs until two reproducible arterial systolic BP responses were obtained. The data obtained during the maneuver were discarded if the subject was unable to maintain a pressure of at least 30 mm Hg for at least 10 seconds. The averages of systolic BP, diastolic BP, and HR were determined for each patient over the 30-second interval directly preceding the VM. The magnitude of BP was determined for four phases as described previously:<sup>22</sup> phase I, early and late phase II, phase III, and phase IV. In subjects with an absent late phase II, the value for early phase II was used instead and the absence noted (zero value). The BP change in each phase was quantified as the difference from the average systolic BP. The pressure recovery time was defined as the time taken for the systolic BP to return from its lowest value during the valley of phase III to baseline before it overshoot during phase IV. The Valsalva ratio was calculated as the ratio between the highest HR generated in phase II and the lowest HR in phase IV, as described previously.<sup>22</sup> In cases where there was a flat-top response during the VM, the test was repeated with the head tilted up by 20° in order to obtain appropriate results. If the appropriate test result could not be acquired, it was ignored as a missing value. All patients with any missing values were excluded from the analyses.

### HUTT

The HUTT was performed using Finometer equipment (Finapres Medical Systems) with a cuff placed on the middle finger and a sphygmomanometer cuff simultaneously placed over the brachial artery. Serial measurements of BP and HR were performed. The systolic and diastolic BPs were displayed on a monitor console. After resting for 20 minutes in a supine position on a standard electrically driven tilt table with a footboard, the baseline BP was measured while simultaneous HR recording was also performed. The table was then tilted for 30 minutes at an angle of 70° from the supine position. The systolic BP, diastolic BP, mean BP, and HR were serially measured every minute for 30 minutes. The resting-state BP and HR were then measured 10 minutes after returning the table to a supine position.

Based on the response pattern to the HUTT, patients were

classified as OH, neurocardiogenic syncope, or postural tachycardia syndrome. Patients were classified as OH if the systolic or diastolic BP had decreased by at least 20 mm Hg or 10 mm Hg, respectively, within 3 minutes after standing up following the HUTT.<sup>23</sup> Patients were classified as having neurocardiogenic syncope when the development of symptoms recognized by the patients was similar to those of spontaneous syncope in association with hypotension, bradycardia, or both.<sup>3</sup> Patients who displayed HR increases of more than 30 beats per minute or a maximum HR of 120 beats per minute within the first 10 minutes without evidence of OH were classified as having postural tachycardia syndrome.<sup>1</sup> Patients were rapidly returned to the supine position as soon as symptoms occurred.

### Statistical analysis and machine learning

Clinical variables and parameters of AFTs were compared between patients with OH and non-OH controls using the chi-squared test or independent *t*-test. Univariate analysis was used to identify the clinical and AFT variables that were associated with OH in logistic regression. Variables found to be possibly significant predictors of OH ( $p < 0.05$ ) in the univariate analysis were entered into a multivariate analysis. Multivariate analyses were conducted using logistic regression to determine the factors independently predicting OH. All patients with any missing values in AFTs were excluded from the analyses. Statistical analyses were performed using SPSS (version 21.0, IBM Corp., Armonk, NY, USA).

Variables found to be possible predictors of OH in the univariate analyses were selected as input features in machine-learning algorithms. Because the purpose of this study was to determine whether OH could be screened based on HR-based parameters that can be obtained without special equipment, the measures from the QSART and from BP responses during the VM are not considered as predictors in the univariate and multivariate analyses. Since the sample sizes of the 2 groups were not balanced (78 OH and 585 non-OH patients), machine-learning algorithms could be skewed toward predicting non-OH. To deal with problems associated with the imbalanced data sets, we modified the training set by downsizing the larger samples.<sup>24</sup> Specifically, 78 non-OH participants were randomly selected using a random-number table from the pool of 585 non-OH participants. The trends of the differences in age, sex, and AFT results between the selected 78 non-OH and 78 OH individuals were the same as those between all 585 non-OH controls and 78 OH patients.

This study evaluated the utility of the selected input features in discriminating the two groups (i.e., OH patients and non-OH controls) by applying three widely used supervised machine-learning techniques: support vector machine (SVM),<sup>25</sup>

*k*-nearest neighbors (KNN),<sup>26</sup> and random forest classifiers.<sup>27</sup> These analyses were carried out using the scikit-learn package written in the Python programming language.<sup>28</sup> Subjects with missing data points were excluded. We evaluated tenfold cross-validations with the proportion of data points from the two classes (i.e., OH and non-OH), controlled to be the same in every partition. The performance of each classifier was evaluated using a confusion matrix containing the following precision, recall, and accuracy parameters:

$$\text{Precision} = \frac{TP}{(TP+FP)},$$

$$\text{Recall} = \frac{TP}{(TP+FN)},$$

$$\text{Accuracy} = \frac{(TP+TN)}{(TP+TN+FP+FN)},$$

where TP, FP, TN, and FN are the numbers of true positives, false positives, true negatives, and false negatives, respectively.

## RESULTS

### Subject characteristics

The results from the HUTTs revealed that 78 of the 719 enrolled OI patients had OH, 30 had neurocardiogenic syncope, 26 had postural tachycardia syndrome, and 585 had none of these conditions, and so 78 HUTT-confirmed OH patients and 585 non-OH controls were included in the statistical analysis. Their demographics, clinical characteristics, and AFT parameters are detailed in Table 1. Compared with controls, OH patients were more likely to be older and hypertensive (both  $p < 0.001$ ). The most-common cause of OH in the 78 patients with OH was Parkinson's disease ( $n=43$ ), followed by multiple-system atrophy ( $n=19$ ) and diabetic neuropathy ( $n=16$ ).

### Comparisons of AFT results and regression analyses

The recorded sweat volume in the proximal foot ( $p=0.013$ ), E-I difference ( $p < 0.001$ ), E:I ratio ( $p < 0.001$ ), and Valsalva ratio ( $p=0.008$ ) were smaller in patients with OH than con-

**Table 1.** Demographics and results of autonomic function tests

	OH patients (n=78)	Non-OH controls (n=585)	p
Age, years	68.1±11.8	57.1±16.6	<0.001
Sex, female	34 (43.6)	288 (49.2)	0.399
Baseline systolic BP, mm Hg	144.7±22.4	130.9±21.9	<0.001
Baseline diastolic BP, mm Hg	69.0±10.3	68.7±9.5	0.810
Baseline HR, bpm	69.0±14.1	68.0±10.6	0.447
QSART sweat volume, μL			
Forearm	1.07±0.89	1.01±1.19	0.672
Proximal leg	1.06±1.38	1.06±1.37	0.981
Distal leg	0.94±0.62	0.97±0.76	0.688
Proximal foot	0.20±0.24	0.28±0.31	0.013
Deep breathing			
Minimum expiration HR, bpm	67.2±15.1	64.9±11.2	0.189
Maximum inspiration HR, bpm	72.8±15.0	74.7±11.3	0.282
E-I difference, bpm	5.6±3.6	9.9±6.9	<0.001
E:I ratio	1.09±0.06	1.16±0.11	<0.001
Valsalva maneuver			
ΔSystolic BP (early phase II), mm Hg	-37.4±19.8	-4.6±12.0	<0.001
ΔSystolic BP (late phase II), mm Hg	-18.8±25.3	6.4±11.6	0.004
ΔSystolic BP (phase IV), mm Hg	22.8±16.6	23.8±15.4	0.869
Valsalva ratio (phase-II HR/phase-IV HR)	1.24±0.16	1.46±0.75	0.008
CASS			
Total score	4.38±1.80	2.09±1.66	<0.001
Sudomotor-domain score	1.50±0.92	1.04±0.91	<0.001
Cardiovagal-domain score	1.18±0.77	0.65±0.70	<0.001
Adrenergic-domain score	1.72±0.97	0.42±0.72	<0.001

Data are mean±SD or *n* (%) values.

BP: blood pressure, CASS: Composite Autonomic Scoring Scale, E-I difference: difference between expiration and inspiration, E:I ratio: expiration:inspiration ratio, HR: heart rate, OH: orthostatic hypotension, QSART: quantitative sudomotor axon reflex test.

**Table 2.** Results from the logistic regression analyses of predicting orthostatic hypotension

	Univariate analysis	<i>p</i>	Multivariate analysis	<i>p</i>
Age	1.057 (1.036–1.079)	<0.001	NS	NS
Male sex	1.255 (0.780–2.020)	0.350	-	-
E-I difference	0.883 (0.835–0.934)	<0.001	NS	NS
E:I ratio	0.000 (0.000–0.004)	<0.001	NS	NS
Valsalva ratio	0.002 (0.000–0.011)	<0.001	0.006 (0.001–0.048)	<0.001
Baseline systolic BP	1.026 (1.016–1.036)	<0.001	1.013 (1.001–1.024)	0.027
Baseline diastolic BP	1.003 (0.979–1.028)	0.809	-	-
Baseline HR	1.008 (0.987–1.029)	0.447	-	-

Data are odds ratio (95% confidence interval) values.

BP: blood pressure, E-I difference: difference between expiration and inspiration, E:I ratio: expiration:inspiration ratio, HR: heart rate, NS: not significant.

trols. The HR during phase IV in the VM was higher in the OH patients than in the controls ( $p=0.025$ ). The decrease in BP during early phase II in the VM was larger in the OH patients than in the controls ( $p<0.001$ ). BP during late phase II in the VM increased in the controls but not in the OH patients ( $p=0.004$ ). The total CASS score and the scores in all of its domains were higher in the OH patients than in the controls (all  $p<0.001$ ).

The results from the univariate and multivariate analyses are summarized in Table 2. Increased age, decreased E-I difference, decreased E:I ratio, decreased Valsalva ratio, and increased baseline systolic BP were found to be associated with predicting OH in the univariate analyses (all  $p<0.001$ ). In the multivariate analyses, a decrease in the Valsalva ratio ( $p<0.001$ ) and an increase in baseline systolic BP ( $p=0.027$ ) were found to independently predict OH.

### Application of machine-learning algorithms

Compared with 78 non-OH controls who were randomly selected to balance the data sets for machine learning, the OH patients were more likely to be older and hypertensive (both  $p<0.001$ ). The E-I difference ( $p<0.001$ ), E:I ratio ( $p<0.001$ ), and Valsalva ratio ( $p=0.016$ ) were smaller in patients with OH than in the 78 non-OH controls. These trends are the same as in comparisons between the 78 OH patients and all 585 non-OH controls. The five variables (i.e., age, baseline systolic BP, E-I difference, E:I ratio, and Valsalva ratio) found to be possible predictors of OH in the univariate analyses were selected for use as input features in machine-learning algorithms. The results obtained using the machine-learning algorithms are presented in Table 3. The accuracies for classifying between OH and non-OH patients were 84.4%, 84.4%, and 90.6% for the SVM, KNN, and random forest methods, respectively.

**Table 3.** Performance of the machine-learning algorithms

Algorithm	Precision	Recall	Accuracy
SVM	0.83	0.88	0.84
KNN	0.83	0.88	0.84
Random forest	0.94	0.88	0.91

KNN: *k*-nearest neighbors, SVM: support vector machine.

## DISCUSSION

We found that age, baseline systolic BP, E-I difference, E:I ratio, and Valsalva ratio are possible predictors for differentiating OH from non-OH patients. Among these five variables, increased baseline systolic BP and a decreased Valsalva ratio were found to be independent predictors of OH. Moreover, we observed that a random forest classifier could distinguish OH from non-OH patients using the five variables with an accuracy of 90.6%.

OI is a main presenting symptom of sympathetic adrenergic failure. In addition, adrenergic dysfunction is considered as a mechanism underlying neurogenic OH that occurs frequently in patients with neurodegenerative disorders.<sup>29</sup> Given that BP and HR responses during the VM as well as during the HUTT are widely used for quantifying adrenergic autonomic function,<sup>30</sup> previous findings of close relationships between BP changes during the VM and HUTT suggest that the VM can be used as a supplementary nonpostural technique to measure baroreflex sensitivity in patients with OI.<sup>13,14</sup> Our findings that HR responses during the VM (i.e., Valsalva ratio) were found to independently predict OH further support this suggestion.

Previous studies have provided valuable information about the utility of BP responses during the VM for diagnosing or differentiating OI,<sup>13,14</sup> but there remains a paucity of studies investigating the usefulness of HR responses during nonpostural stimuli (including the VM and deep breathing) for diagnosing OH. We found that OH patients exhibit decreases in HR responses during the VM (i.e., Valsalva

ratio) and deep breathing (i.e., E-I difference and E:I ratio) relative to non-OH controls. Moreover, we identified that the accuracy of a random forest algorithm for differentiating OH from non-OH patients using the variables without postural stimuli was more than 90%. Our findings suggest that HR changes during nonpostural stimuli, including VM and deep breathing, might be an important marker for diagnosing OH in patients with OI.

While OH is a well-known manifestation of adrenergic sympathetic dysfunction, our findings of decreases in E-I difference, E:I ratio, and Valsalva ratio indicated that the patients with OH also had cardiovagal parasympathetic dysfunction.<sup>30</sup> The mechanisms underlying impairments of autonomic function encompassing the adrenergic sympathetic and cardiovagal domains in patients with OH are not fully understood. However, they might be partly explained by parasympathetic function usually being impaired before sympathetic function in disorders involving the autonomic nervous system.<sup>31</sup> Based on the sequential pattern of progression of autonomic dysfunction, our results further support the hypothesis that parameters reflecting cardiovagal function can be used as sensitive screening measurements for sympathetic dysfunction.<sup>31</sup>

Previous studies utilized the pulse transit time (PTT) as a surrogate marker for BP changes, since wearable devices can measure BP continuously and conveniently.<sup>32,33</sup> However, PTT-based BP estimation might not be reliable in patients with atherosclerotic arterial stiffness and cardiac arrhythmia.<sup>34,35</sup> Considering that elderly OH patients usually have cardiovascular comorbidities, PTT-based BP measurements by wearable devices might be restricted in identifying the presence of OH. In our study, the parameters used in the highly accurate predictive algorithm were mainly based on the HR, and so HR-based algorithms for screening OH could be easily applied when special equipment such as a tilt table and Finometer are not available. Moreover, since the VM and deep breathing can be easily applied by patients themselves as nonpostural stimuli, our findings may represent evidence for the utility of using HR-based algorithm-embedded wearable devices to diagnose OH.

It remains unclear how the HR-based algorithm predicts OH with high accuracy. Heart rate variability (HRV) has been widely used for quantifying sympathetic and parasympathetic activities through time- and frequency-domain parameters.<sup>36</sup> A plausible explanation for the high accuracy of the HR-based algorithm in predicting OH is that HR responses during deep breathing and during the VM act as sensitive predictors in the same way as time-domain HRV parameters. Further study is needed to understand the mechanisms underlying how HR-based parameters can be used to predict OH with high accu-

racy in machine-learning algorithms.

There are several limitations of the present study that should be considered when interpreting our results. First, only subjects who were referred to a university-affiliated hospital with a relatively small patient population were included in this study. This restricts the ability to generalize our findings to the entire OH population. Second, the OH patients and non-OH controls were not matched for age, and so the higher incidence of comorbidities in elderly patients with OH might have confounded the results of the AFTs. Finally, a flat-top response during the VM can appear in patients with a cardiac problem, and appropriate test results cannot be obtained even after repeating the maneuvers with the head tilted up by 20°. This might prevent implementing the VM to derive the parameters that are applicable to the algorithm.

We have found that age, baseline systolic BP, E-I difference, E:I ratio, and Valsalva ratio could be alternatives to the HUTT for predicting OH. In addition, machine-learning algorithms using these five parameters as input features were highly accurate in differentiating OH from non-OH patients. Given the poor reproducibility and low sensitivity of the HUTT,<sup>37,38</sup> machine-learning algorithms using these features might be a useful screening tool for diagnosing OH before performing the HUTT. Future prospective studies with large populations are required to verify the reliability of applying machine-learning algorithms to diagnose OH based on variables obtained without special equipment.

#### Author Contributions

Conceptualization: Jung Bin Kim, Byung-Jo Kim. Data curation: Hayom Kim, Joo Hye Sung. Formal analysis: Jung Bin Kim. Investigation: Seol-Hee Baek. Methodology: Jung Bin Kim. Supervision: Byung-Jo Kim. Writing—original draft: Jung Bin Kim, Hayom Kim. Writing—review & editing: Byung-Jo Kim.

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#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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#### REFERENCES

- Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biagioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011;21:69-72.

2. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007;120:841-847.
3. Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS), Moya A, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;30:2631-2671.
4. Veronese N, De Rui M, Bolzetta F, Zambon S, Corti MC, Baggio G, et al. Orthostatic changes in blood pressure and mortality in the elderly: the pro.V.A study. *Am J Hypertens* 2015;28:1248-1256.
5. Angelousi A, Giererd N, Benetos A, Frimat L, Gautier S, Weryha G, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens* 2014;32:1562-1571.
6. Mol A, Bui Hoang PTS, Sharmin S, Reijnierse EM, van Wezel RJA, Meskers CGM, et al. Orthostatic hypotension and falls in older adults: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2019;20:589-597.e5.
7. Iseli R, Nguyen VTV, Sharmin S, Reijnierse EM, Lim WK, Maier AB. Orthostatic hypotension and cognition in older adults: a systematic review and meta-analysis. *Exp Gerontol* 2019;120:40-49.
8. Shaw BH, Borrel D, Sabbaghan K, Kum C, Yang Y, Robinovitch SN, et al. Relationships between orthostatic hypotension, frailty, falling and mortality in elderly care home residents. *BMC Geriatr* 2019;19:80.
9. Fleg JL, Evans GW, Margolis KL, Barzilay J, Basile JN, Bigger JT, et al. Orthostatic Hypotension in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial: prevalence, incidence, and prognostic significance. *Hypertension* 2016;68:888-895.
10. Parry SW, Reeve P, Lawson J, Shaw FE, Davison J, Norton M, et al. The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders. *Heart* 2009;95:416-420.
11. Kim JB, Hong S, Park JW, Cho DH, Park KJ, Kim BJ. Utility of corrected QT interval in orthostatic intolerance. *PLoS One* 2014;9:e106417.
12. Kim YH, Phillips V Z, Paik SH, Jeon NJ, Kim BM, Kim BJ. Prefrontal hemodynamic changes measured using near-infrared spectroscopy during the Valsalva maneuver in patients with orthostatic intolerance. *Neurophotonics* 2018;5:015002.
13. Kim HA, Yi HA, Hong JH, Lee H. Detailed relationship between the pattern of blood pressure change during the valsalva maneuver and the degree of orthostatic hypotension during the head-up tilt test in patients with orthostatic intolerance: a retrospective case-control study. *Medicine (Baltimore)* 2016;95:e3608.
14. Palamarchuk IS, Baker J, Kimpinski K. The utility of Valsalva maneuver in the diagnoses of orthostatic disorders. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R243-R252.
15. Lee SP, Ha G, Wright DE, Ma Y, Sen-Gupta E, Haubrich NR, et al. Highly flexible, wearable, and disposable cardiac biosensors for remote and ambulatory monitoring. *NPJ Digit Med* 2018;1:2.
16. Seok HY, Kim YH, Kim H, Kim BJ. Patterns of orthostatic blood pressure changes in patients with orthostatic hypotension. *J Clin Neurol* 2018;14:283-290.
17. Koo YS, Cho CS, Kim BJ. Pitfalls in using electrophysiological studies to diagnose neuromuscular disorders. *J Clin Neurol* 2012;8:1-14.
18. Kim JB, Kim BJ, Koh SB, Park KW. Autonomic dysfunction according to disease progression in Parkinson's disease. *Parkinsonism Relat Disord* 2014;20:303-307.
19. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc* 1993;68:748-752.
20. Low PA. Autonomic nervous system function. *J Clin Neurophysiol* 1993;10:14-27.
21. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. *Muscle Nerve* 1997;20:1561-1568.
22. Vogel ER, Sandroni P, Low PA. Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. *Neurology* 2005;65:1533-1537.
23. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.
24. Kubat M, Matwin S. *Addressing the curse of imbalanced training sets: one-sided selection*. Proceedings of the Fourteenth International Conference on Machine Learning; 1997 Jul 8-12, Nashville, TN, USA: 179-186.
25. Cortes C, Vapnik V. Support-vector networks. *Mach Learn* 1995;20:273-297.
26. Weinberger KQ, Blitzer J, Saul LK. Distance metric learning for large margin nearest neighbor classification. In: Weiss Y, Schölkopf B, Platt J, editors. *Advances in Neural Information Processing Systems 18*. Cambridge, MA: MIT Press, 2006;1473-1480.
27. Liaw A, Wiener M. Classification and regression by randomForest. *R News* 2002;2:18-22.
28. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: machine learning in Python. *J Mach Learn Res* 2011;12:2825-2830.
29. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. *Lancet Neurol* 2008;7:451-458.
30. Low PA, Tomalia VA, Park KJ. Autonomic function tests: some clinical applications. *J Clin Neurol* 2013;9:1-8.
31. Shields RW Jr. Heart rate variability with deep breathing as a clinical test of cardiovagal function. *Cleve Clin J Med* 2009;76 Suppl 2:S37-S40.
32. Padilla JM, Berjano EJ, Saiz J, Facila L, Diaz P, Merce S. *Assessment of relationships between blood pressure, pulse wave velocity and digital volume pulse*. Proceedings of 2006 Computers in Cardiology; 2006 Sep 17-20; Valencia, Spain. Piscataway, NJ: IEEE; 2006:893-896.
33. Chandrasekaran V, Dantu R, Jonnada S, Thiyagaraja S, Subbu KP. Cuffless differential blood pressure estimation using smart phones. *IEEE Trans Biomed Eng* 2013;60:1080-1089.
34. Jones DW, Appel LJ, Sheps SG, Roccella EJ, Lenfant C. Measuring blood pressure accurately: new and persistent challenges. *JAMA* 2003;289:1027-1030.
35. Beevers G, Lip GY, O'Brien E. ABC of hypertension: blood pressure measurement. Part II-conventional sphygmomanometry: technique of auscultatory blood pressure measurement. *BMJ* 2001;322:1043-1047.
36. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput* 2006;44:1031-1051.
37. Grubb BP, Kosinski D. Tilt table testing: concepts and limitations. *Pacing Clin Electrophysiol* 1997;20:781-787.
38. Ward C, Kenny RA. Reproducibility of orthostatic hypotension in symptomatic elderly. *Am J Med* 1996;100:418-422.