Influencing factors and hemodynamic study of initial and sustained orthostatic hypotension in middle-aged and elderly patients

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Abstract
Orthostatic hypotension (OH) is a common autonomic disorder. This study aimed to investigate the influencing factors and hemodynamic mechanisms of initial and sustained OH in middle-aged and elderly patients. The authors analyzed the clinical characteristics and hemodynamic variables of patients aged ≥50 years according to the various forms of OH, diagnosed by an active orthostatic test using the CNAP monitor. The study included 473 participants; 119 (25.2%) patients had initial (54, 45.4%) or sustained (65, 54.6%) OH. Age, comorbidities, or medications did not differ significantly between the initial OH and non-OH groups. Sustained OH was associated with age and diabetes (p=0.003 and p=0.015, respectively). Hemodynamic analysis revealed higher cardiac output (CO) in the sustained OH group within 15 s than in the non-OH and initial OH groups (both p<0.001); no difference in CO was observed between the initial OH and non-OH groups. The systemic vascular resistance (SVR) in both initial OH and sustained OH groups within 15 s was lower than that in the non-OH group (both p<0.001). No differences in SVR at 3 min were observed between the initial OH and non-OH groups. The SVR at 3 min in the sustained OH group was significantly lower than in non-OH and initial OH groups (both p<0.001). Age and diabetes emerged as the independent risk factors associated with sustained OH. Initial OH is associated with a mismatch of increase in CO and decrease in SVR. Sustained OH is mainly associated with sustained inadequate adjustment in SVR.

KEYWORDS
cardiac output, initial orthostatic hypotension, middle-aged and elderly patients, orthostatic hypotension, sustained orthostatic hypotension, systemic vascular resistance
Orthostatic hypotension (OH) is an important medical problem that is particularly common in elderly patients with multiple comorbidities and polypharmacy. Classic OH is defined as a sustained reduction in systolic blood pressure (BP) by at least 20 mm Hg and/or reduction in diastolic BP by 10 mm Hg within 3 min of standing or 60° head-up tilt. These criteria were originally defined in 1996 in a consensus statement sponsored by the American Autonomic Society and the American Academy of Neurology. Over the past years, continuous noninvasive BP monitoring systems, such as the CNAP monitor (CN Systems Medizintechnik AG, Graz, Austria), have enabled clinicians to observe rapid changes in BP. In 2011, the consensus statement was expanded to include initial OH, defined as a transient BP decrease (> 40 mm Hg systolic and/or > 20 mm Hg diastolic BP within 15 s of standing). By definition, the hallmark of initial OH is its immediate and transient nature, which is also the key feature that makes it different from classical OH. Although such rapid changes in BP are barely detectable by intermittent upper-arm BP measurement, beat-to-beat BP measurement increases the diagnosis rate of initial OH. Presently, limited data are available regarding the initial and sustained OH in middle-aged and elderly patients and their hemodynamic changes. Therefore, this study aimed to gain insights into the characteristics and underlying hemodynamic mechanisms of initial and sustained OH in middle-aged and elderly patients through continuous noninvasive BP monitoring.

2 | METHODS

2.1 | Participants

This study was conducted in the geriatric cardiovascular department of a tertiary teaching hospital between January 2017 and April 2018. During this period, all consecutive patients hospitalized in the geriatric cardiovascular department were screened. The inclusion criteria were as follows: (1) patients aged ≥ 50 years (in both sexes); (2) those who had the ability to stand up actively from the supine position and keep fit for 3 min; and (3) those who had the ability to cooperate well with the measurements by the CNAP monitor. Patients were excluded if they (1) were unable to stand for 3 min; (2) needed immediate treatment; (3) had a cognitive disorder, thus were not able to provide informed consent; and (4) had irregular heart rhythm such as atrial fibrillation. This study was approved by the institutional review board and ethics committee of the participating center (registration number: 2017[1351]). Informed consent was obtained from all the participants. Data from the participants and investigators were anonymized.

2.2 | Protocol

Patients’ demographic information, medical comorbidities, medications, and associated clinical data were extracted from the medical records in the geriatric cardiovascular department during the study period. The diagnoses of hypertension, coronary heart disease, dyslipidemia, and diabetes mellitus were conducted according to the associated guidelines. All participants underwent measurement of body mass index (BMI) and brachial-ankle pulse wave velocity (baPWV) during their hospitalization. The baPWV was automatically measured by two trained researchers using form PWV/ABI instruments (form PWV/ABI, BP-203RPE III; Omron-Colin, Japan).

For continuous measurements, a CNAP monitor (CN Systems Medizintechnik AG, Graz, Austria), which is a continuous noninvasive arterial pressure measurement device, was used. Based on the volume clamp method, this device monitors the blood flowing (measured by light absorption) into the finger and translates blood flow oscillations sensed by the encircling finger cuff into continuous pulse pressure waveforms and beat-to-beat BP values. This is analyzed using a proprietary algorithm to estimate hemodynamic parameters such as cardiac output (CO) and systemic vascular resistance (SVR). The CNAP monitor has been validated for arterial BP and CO measurements.

Continuous noninvasive orthostatic BP measurements were performed by two fixed trained researchers. The orthostatic test was assessed by actively standing up for 3 min after a 5-min supine resting period. All orthostatic tests were conducted between 9:00–11:00 a.m. and 2:00–5:00 p.m. during the day, and more than 2 h after meals to avoid possible interference with postprandial hypotension. An appropriately sized finger cuff of the CNAP monitor was affixed to each participant’s finger, and the measurement hand was placed at the heart level. The beat-to-beat measurements of systolic BP, diastolic BP, heart rate (HR), CO, and SVR of all participants were performed in the supine position and within 15 s and 3 min after active standing. Subsequently, patients were asked if they had experienced any symptoms, such as lightheadedness or seeing black spots while standing. Initial OH was defined as a transient decrease in systolic BP by > 40 mm Hg and/or diastolic BP by > 20 mm Hg within 15 s of active standing, with BP recovery between 15 s and 3 min of standing (decrease in systolic BP < 20 mm Hg and diastolic BP < 10 mm Hg). Sustained OH was defined as a sustained decrease in systolic BP by ≥ 20 mm Hg and/or diastolic BP by ≥ 10 mm Hg at 3 min after standing. Changes in BP that met the definition of either initial or sustained OH were defined as OH.

2.3 | Statistical analysis

IBM SPSS (version 22.0; IBM Corp, Armonk, NY, USA) was used for the statistical analyses. The main characteristics of the study population are presented as mean ± standard deviation for normally distributed continuous variables and percentages for categorical variables. Significant differences in the continuous data between the two groups of variables were evaluated using a two-tailed independent t-test. Inter-group differences were analyzed using ANOVA for non-categorical variables and Pearson’s chi-square test for categorical variables. Multivariate binary logistic regression analyses were performed to identify the variables associated with OH risk. The actual p-values are provided,
and a p-value < .05 was considered to indicate a statistically significant difference.

3 | RESULTS

Of the 645 patients hospitalized during the study period, 56 could not stand for 3 min or needed immediate treatment, 18 had a cognitive disorder and were not able to provide informed consent, 50 had an irregular heart rhythm, and 48 did not undergo the orthostatic test. Finally, 473 patients were included, all of whom underwent measurements after active standing. The mean age was 70.4 ± 12.7 years, and 75.7% were male. A total of 119 (25.2%) patients had OH (initial or sustained), and among them, 54 (45.4%) had initial OH, and 65 (54.6%) had sustained OH. Twenty-one of the 65 patients with sustained OH had a decrease of > 40 mm Hg in systolic BP and/or > 20 mm Hg in diastolic BP within 15 s of active standing.

3.1 | Influencing factors of initial and sustained OH

No significant differences in sex, BMI, medical history of dyslipidemia, or antihypertensive medication use were observed between the non-OH, initial OH, and sustained OH groups (p-values > .05). In contrast, significant differences were observed in age, baPWV, and comorbidity of hypertension, coronary heart disease, and diabetes among the groups (p = .001, .028, .028, .005, and .035, respectively). Compared to patients in the non-OH and initial OH groups, patients with sustained OH were older (75.7 ± 11.3 vs. 69.8 ± 12.3 years; p < .001 and 75.7 ± 11.3 vs. 67.9 ± 15.2 years; p = .002), more likely to have comorbid hypertension (83.1% vs. 71.2%; p = .049 and 83.1% vs. 61.1%; p = .012) and diabetes (52.3% vs. 31.6%; p = .002 and 52.3% vs. 31.5%; p = .026), and had a higher baPWV (17.8 ± 3.1 vs. 16.7 ± 3.4 m/s; p = .022 and 17.8 ± 3.1 vs. 16.3 ± 3.1 m/s; p = .016). In addition, coronary heart disease was more common in patients with sustained OH than in those with initial OH (61.5% vs. 37.0%; p = .010). However, no significant differences were observed in any of the factors mentioned above between the initial OH and non-OH groups (p > .05) (Table 1). Symptoms of OH were more common in patients with sustained OH than in those without OH and with initial OH (p < .001 and p = .013) (Table 1).

Further, binary regression analysis showed that sustained OH was positively associated with age and diabetes (odds ratio [OR] = 1.040, 95% confidence interval [CI]: 1.014–1.068; p = .003 and OR = 2.009, 95% CI: 1.147–3.517; p = .015). However, hypertension and baPWV were no longer associated with sustained OH after adjusting for other influencing factors (p > .05) (Table 2).

3.2 | Hemodynamic study of initial and sustained OH

The hemodynamic variables measured are shown in Table 3. In the supine position, no significant differences in CO, SVR, diastolic BP, or HR were observed among the three groups; however, systolic BP was higher in the sustained OH group than in the non-OH and initial OH groups (128 ± 18 vs. 118 ± 16 mm Hg; p < .001 and 128 ± 18 vs. 117 ± 13 mm Hg; p < .001). During the orthostatic test, the measurements of systolic and diastolic BP within 15 s in the initial OH group were significantly lower than those in the non-OH (88 ± 16 vs. 109 ± 21 mm Hg; p < .001 and 47 ± 8 vs. 64 ± 12 mm Hg; p < .001) and sustained OH (88 ± 16 vs. 104 ± 20 mm Hg; p < .001 and 47 ± 8 vs. 53 ± 11 mm Hg; p = .004) groups. The measurements of systolic and diastolic BP at 3 min in the sustained OH group were significantly lower than those in the non-OH (109 ± 18 vs. 123 ± 20 mm Hg; p < .001 and 57 ± 9 vs. 75 ± 13 mm Hg; p < .001) and initial OH (109 ± 18 vs. 118 ± 18 mm Hg; p = .015 and 57 ± 9 vs. 72 ± 10 mm Hg; p < .001) groups.

Hemodynamic analysis showed that the CO values of the sustained OH group within 15 s were significantly higher than those of the non-OH and initial OH groups (5.3 ± 1.2 vs. 4.8 ± 1.1 L/min; p = .002 and 5.3 ± 1.2 vs. 4.8 ± 1.9 L/min; p = .016), while no difference in the CO values was seen between the initial OH and non-OH groups (p > .05). The SVR measurements within 15 s of both the initial OH and sustained OH groups were significantly lower than those of the non-OH group (1216 ± 297 vs. 1352 ± 332 dynes-sec-cm⁻²; p = .007 and 1175 ± 347 vs. 1352 ± 332 dynes-sec-cm⁻²; p < .001). However, no significant differences were observed in SVR values at 3 min between the initial OH and non-OH groups (p > .05); whereas the SVR values of the sustained OH group were still significantly lower at 3 min during the orthostatic test than those of the non-OH and initial OH groups (1140 ± 320 vs. 1475 ± 379 dynes-sec-cm⁻²; p < .001 and 1140 ± 320 vs. 1378 ± 326 dynes-sec-cm⁻²; p = .001). Furthermore, the HR measurements showed no significant differences during the orthostatic test among the three groups (p > .05) (Table 3).

4 | DISCUSSION

Our study results show that OH is common in middle-aged and elderly patients and is present in up to 25.2% of our studied patients, among whom 45.4% had initial OH and 54.6% had sustained OH. According to previous studies, OH is seen in 19%–68% of older inpatients, and the prevalence of initial OH ranges from 3.5% to 62.5% in geriatric patients aged ≥ 65 years, depending on the population characteristics, comorbidities, and medications.

Many previous studies have shown that the prevalence of OH increases with advancement in age, partly due to a normal physiological decline in baroreceptor sensitivity and partly due to the age-associated increased prevalence of autonomic neurodegenerative diseases. In our study, we observed a positive relationship between sustained OH and age, whereas no significant association was observed between initial OH and age. Finucane and coworkers explored the prevalence of initial OH and classic OH in an Irish longitudinal study on aging (TILDA) and showed that the prevalence of classic OH increased with age, while initial OH showed no evident age gradient. Individuals in whom orthostatic BP reduction takes more time to recover to the
TABLE 1  Clinical characteristics of patients stratified by the presence of various forms of OH

| Variable                      | Non-OH (n = 354) | Initial OH (n = 54) | Sustained OH (n = 65) | Overall p-value |
|-------------------------------|------------------|---------------------|-----------------------|-----------------|
| **Demographic**               |                  |                     |                       |                 |
| Male, n (%)                   | 271 (76.5)       | 41 (75.9)           | 46 (70.8)             | .606            |
| Age, years                    | 69.8 ± 12.3b     | 67.9 ± 15.2c        | 75.7 ± 11.3b,c        | .001            |
| **Comorbid diseases, n (%)**  |                  |                     |                       |                 |
| Hypertension                  | 252 (71.2) b     | 33 (61.1) c         | 54 (83.1) b,c         | .028            |
| Coronary heart disease        | 183 (51.7)       | 20 (37.0) c         | 40 (61.5) c           | .028            |
| Dyslipidemia                  | 279 (78.8)       | 40 (74.1)           | 46 (70.8)             | .309            |
| Diabetes mellitus             | 112 (31.6) b     | 17 (31.5) c         | 34 (52.3) b,c         | .005            |
| **Medications, n (%)**        |                  |                     |                       |                 |
| ACEI/ARB                      | 158 (44.6)       | 18 (33.3)           | 28 (43.1)             | .295            |
| Beta-blockers                 | 182 (51.4)       | 27 (50.0)           | 34 (52.3)             | .969            |
| Calcium antagonists           | 129 (36.4)       | 16 (29.6)           | 23 (35.4)             | .622            |
| Diuretics                     | 35 (9.9)         | 2 (3.7)             | 10 (15.4)             | .105            |
| Alpha-receptor blockers       | 56 (15.8)        | 9 (16.7)            | 17 (26.2)             | .128            |
| **Clinical parameters**       |                  |                     |                       |                 |
| BMI (kg/m²)                   | 25.0 ± 3.2       | 24.8 ± 3.1          | 24.7 ± 3.9            | .707            |
| baPWV (m/s)                   | 16.7 ± 3.4b      | 16.3 ± 3.1c         | 17.8 ± 3.1b,c         | .035            |
| Symptoms of OH                | 16 (4.5) b       | 6 (11.1) c          | 20 (30.8) b,c         | <.001           |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; baPWV, brachial-ankle pulse wave velocity.

aSignificant difference between non-OH and initial OH.
bSignificant difference between non-OH and sustained OH.
cSignificant difference between initial OH and sustained OH.

TABLE 2  Multiple regression analysis for influencing factors of sustained OH

|          | B     | SE    | OR   | 95% CI | p     |
|----------|-------|-------|------|--------|-------|
| Age      | .039  | .013  | 1.040| 1.014–1.068| .003  |
| diabetes | .697  | .286  | 2.009| 1.147–3.517| .015  |
| hypertension | .382  | .383  | 1.465| .692–3.101| .318  |
| baPWV    | .001  | .001  | 1.000| .999–1.001| .843  |

Abbreviations: OR, odds ratio; CI, confidence interval; baPWV, brachial-ankle pulse wave velocity.

normal level are frailer than those in whom BP recovers quickly (as in initial OH).15

Our study showed that the risk of sustained OH was higher in patients with diabetes, thereby supporting the concept that the prevalence of OH depends on autonomic neuropathy,13 since OH is a common clinical manifestation of diabetic autonomic neuropathy.16–18 Unexpectedly, no relationship was observed between initial OH and comorbidities. Previous studies have focused mostly on classic sustained OH and seldom included initial OH. Finucane and coworkers conducted a nationally representative longitudinal cohort study with a 2-year follow-up. The study showed that initial OH was neither associated with a disease state, nor did it appear to predict an increased fall risk, whereas sustained OH was associated with all-cause falls.19

The ability to recover rapidly from initial OH appears to be a marker of physical fitness, but the delayed recovery from orthostatic BP changes, which is associated with an increased risk of falls, cognitive impairment, and frailty, is a major problem.15 Our study also revealed that OH symptoms were more common in patients with sustained OH.

Community studies have shown that OH is associated with medications, such as antihypertensive drugs, in elderly individuals, although the association is slightly attenuated after adjusting for age and comorbidities.20 Diuretics and α-receptor blockers are considered risk factors for OH, mainly due to their volume depletion and reduced vascular resistance effects.13 Data on calcium channel blockers and β-blockers as risk factors for OH are conflicting.13,21 Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are...
not associated with OH.\textsuperscript{22} Notably, our study sample size was limited, and the number of patients taking diuretics and $\alpha$-receptors was relatively low because we had already avoided prescribing such medication to frail patients in the geriatric ward, which may be the reason why our results did not show any noticeable association between use of diuretics and $\alpha$-receptors and sustained OH.

The transition from the supine to an upright position is accompanied by the redistribution of intravascular volume due to gravity. The shift in blood volume causes a decrease in venous return, stroke volume, and subsequently, arterial pressure. Consequently, the change in arterial pressure activates the baroreflex, which evokes rapid changes in central activity to maintain cardiovascular homeostasis by modulating CO and peripheral vascular resistance.\textsuperscript{12} Previous studies in healthy teenagers and young adult patients using beat-to-beat measurements in suspected (pre)syncope patients older than 18 years and found that CO is the main determinant in the pronounced dynamic changes in suspected (pre)syncope patients older than 18 years and found that CO is the main determinant in the pronounced dynamic characteristics of various types of OH in middle-aged and elderly patients. Initial OH is associated with a mismatch of an increase in CO and a decrease in SVR, while sustained OH is mainly associated with sustained inadequate adjustment in SVR.

At 3 min of the orthostatic test, the SVR as well as the BP measurements in patients with initial OH recovered to the same level as those in patients in the non-OH group. In contrast, the SVR values in patients with sustained OH were still significantly lower, continuing to 3 min after standing, than that in patients without OH and with initial OH. A study conducted by van Wijnen and coworkers compared hemodynamic changes in suspected (pre)syncope patients older than 18 years and found that CO is the main determinant in the pronounced decrease in BP upon standing in patients with initial OH, while delayed BP recovery was associated with an impaired increase in SVR in a significant proportion of individuals.\textsuperscript{24} Previous hemodynamic studies have focused on youth, and only a few involved older individuals. The findings of our study have shown, for the first time, the hemodynamic characteristics of various types of OH in middle-aged and elderly patients. Initial OH is associated with a mismatch of an increase in CO and a decrease in SVR, while sustained OH is mainly associated with sustained inadequate adjustment in SVR.

In our study, no significant increase in HR was observed with initial or sustained OH. A fall in BP is often compensated by a marked increase in HR in non-neurogenic OH through baroreflex activation.\textsuperscript{25} However, when OH is caused by neurodegenerative, metabolic, or autoimmune disorders affecting autonomic function, which are more common in middle-aged and elderly individuals, the orthostatic HR response to

### Table 3

Comparison of hemodynamic data between patients with initial and sustained OH

| Variable          | Non-OH ($n = 354$) | Initial OH ($n = 54$) | Sustained OH ($n = 65$) | Overall p-value |
|-------------------|---------------------|-----------------------|-------------------------|-----------------|
| **CO (L/min)**    |                     |                       |                         |                 |
| Supine            | $4.6 \pm 1.0$       | $4.4 \pm 0.9$         | $4.8 \pm 0.9$           | $0.092$         |
| Within 15 s       | $4.8 \pm 1.1$       | $4.8 \pm 0.9$         | $5.3 \pm 1.2$           | $0.008$         |
| at 3 min          | $4.9 \pm 2.8$       | $4.8 \pm 1.0$         | $5.1 \pm 1.3$           | $0.728$         |
| **SVR (dynes-sec-cm$^{-5}$)** |                     |                       |                         |                 |
| Supine            | $1445 \pm 321$      | $1472 \pm 338$        | $1428 \pm 306$          | $0.757$         |
| Within 15 s       | $1352 \pm 332$      | $1216 \pm 297$        | $1175 \pm 347$          | $<0.001$        |
| at 3 min          | $1475 \pm 379$      | $1378 \pm 326$        | $1140 \pm 320$          | $<0.001$        |
| **Systolic BP (mm Hg)** |                     |                       |                         |                 |
| Supine            | $118 \pm 16$        | $117 \pm 13$          | $128 \pm 18$            | $<0.001$        |
| Within 15 s       | $109 \pm 21$        | $88 \pm 16$           | $104 \pm 20$            | $<0.001$        |
| at 3 min          | $123 \pm 20$        | $118 \pm 18$          | $109 \pm 18$            | $<0.001$        |
| **Diastolic BP (mm Hg)** |                     |                       |                         |                 |
| Supine            | $69 \pm 9$          | $71 \pm 7$            | $69 \pm 9$              | $0.404$         |
| Within 15 s       | $64 \pm 12$         | $47 \pm 8$            | $53 \pm 11$             | $<0.001$        |
| at 3 min          | $75 \pm 13$         | $72 \pm 10$           | $57 \pm 9$              | $<0.001$        |
| **HR (beats/min)** |                     |                       |                         |                 |
| Supine            | $66 \pm 10$         | $65 \pm 11$           | $65 \pm 10$             | $0.929$         |
| Within 15 s       | $75 \pm 12$         | $77 \pm 14$           | $74 \pm 12$             | $0.325$         |
| at 3 min          | $73 \pm 11$         | $74 \pm 12$           | $71 \pm 12$             | $0.309$         |

Abbreviations: OH, orthostatic hypotension; CO, cardiac output; SVR, systemic vascular resistance; BP, blood pressure; HR, heart rate.

\textsuperscript{a}Significant difference between non-OH and initial OH.

\textsuperscript{b}Significant difference between non-OH and sustained OH.

\textsuperscript{c}Significant difference between initial OH and sustained OH.
hypotension may be reduced or absent. In addition, approximately 50% of the patients in our study had taken beta-blockers, which might also influence the rise in HR. Our study had some limitations. First, the participants were patients hospitalized in the geriatric cardiovascular department. Although we documented a systematic evaluation of combined internal medicine diseases; however, we did not evaluate neurological diseases, such as Parkinson’s disease and dementia, which may also be associated with OH. Second, the patients with OH in the present study were simply categorized into initial and sustained OH groups, which might have underestimated the incidence of OH according to the definition of classic OH. Moreover, we did not discuss the “combination” of both the initial and sustained OH. Finally, this was a cross-sectional study, and further follow-up of the study population is needed to provide longitudinal information.

5 | CONCLUSIONS

Our study suggests that the independent risk factors associated with sustained OH are age and diabetes, whereas no significant associations were observed between initial OH and age or comorbidities. The underlying hemodynamic patterns following active standing are heterogeneous and differ across the OH types in middle-aged and elderly patients. Initial OH is associated with a mismatch of an increase in CO and a decrease in SVR, while sustained OH is mainly associated with sustained inadequate adjustment in SVR. Therefore, gaining insights into the different characteristics and hemodynamic mechanisms of initial and sustained OH may help in choosing the appropriate therapies for patients with OH.

AUTHOR CONTRIBUTIONS

Geng Hui, Chen Xiahuan and Liu Meilin contributed to the conception and design of the study. Geng Hui and Wang Yanjun contributed to data collection. Geng Hui performed the data analyses. Geng Hui wrote the main manuscript text and prepared the tables. Liu Meilin supervised the project. Liu Meilin and Liang Wenyi participated in the revision of the manuscript. The authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no competing interests.

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