

Orthostatic blood pressure recovery associates with physical performance, frailty and number of falls in geriatric outpatients

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Objective: Blood pressure (BP) recovery after orthostatic hypotension might be important to prevent cerebral hypoperfusion episodes in older adults, and be related to better clinical outcome. The objective was to study the relationship between BP recovery and clinical outcome, that is physical and cognitive performance, frailty and falls, in geriatric outpatients.

Methods: One hundred and sixty-eight geriatric outpatients underwent continuous (beat-to-beat) BP measurements during standing up, and a comprehensive geriatric assessment, including assessment of physical performance (chair stand test), cognitive performance (Mini Mental State Examination), frailty (Fried criteria) and falls in the previous year. BP recovery was evaluated at 15–30, 30–60, 60–120 and 120–180 s after standing up and defined as mean SBP and DBP in the respective time intervals minus baseline BP. Associations with clinical outcome were assessed using linear (physical and cognitive performance and frailty) and logistic (falls) regression, adjusting for age, sex, baseline BP and initial BP drop.

Results: SBP recovery was associated with frailty (30–60 s interval; $\beta = 0.013$, $P = 0.02$) and falls (30–60 s interval; odds ratio = 1.024, $P = 0.02$). DBP recovery was associated with physical performance (30–60 s interval; $\beta = 0.215$, $P = 0.01$), frailty (30–60 s interval; $\beta = 0.028$, $P = 0.02$) and falls (30–60 s interval; odds ratio = 1.039, $P = 0.04$). Neither SBP nor DBP recovery was associated with cognitive performance.

Conclusion: DBP recovery was particularly associated with clinical outcome in geriatric outpatients, suggesting BP recovery to be of clinical interest.

Keywords: blood pressure determination, cardiovascular system, cognition, falls, frailty, hypotension, orthostatic hypotension, physical functional performance

Abbreviations: BP, blood pressure; IQR, interquartile range; MMSE, Mini Mental State Examination; NIRS, near-infrared spectroscopy; SD, standard deviation

clinical outcome such as poor physical and cognitive performance, cardiovascular diseases, falls and mortality [1–6]. Brain hypoperfusion might act as a mediator in this relationship, potentially causing episodes of acute cerebral oxygen deficit directly after standing up and chronic brain lesions if these episodes are recurrent [7–13]. The adequacy of brain perfusion after standing up may be determined by BP recovery after the orthostatic BP drop, that is the difference between BP after standing up and baseline (i.e. supine) BP as a function of time.

Existing studies are inconclusive with respect to the association between BP recovery after orthostatic hypotension and clinical outcome, partly due to the lack of consensus about BP recovery measures. BP recovery defined as the percentage of baseline BP that is recovered was found to be associated with mortality, only when assessed between 15–20 s after standing up [14]. Impaired BP recovery defined as a BP below the orthostatic hypotension criteria at least at 60–110 s after standing, evaluated every 10 s, was reported to be associated with falls [15,16]. The recovery of SBP at 30, 60 and 180 s after standing up was used in some studies to classify a patient into one of four BP recovery categories [17–19]. In some other studies, BP recovery patterns were clustered using a k-means algorithm, but no association with cognitive performance or comorbidity was found [20,21]. The different BP recovery measures have not been assessed systematically in the same population with respect

Journal of Hypertension 2021, 39:101–106

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Received 18 May 2020 **Revised** 26 June 2020 **Accepted** 15 July 2020

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DOI:10.1097/HJH.0000000000002617

INTRODUCTION

Orthostatic hypotension, defined as a sustained SBP drop more than 20 mmHg or a DBP drop more than 10 mmHg within 3 min after orthostasis, is a prevalent disease in older adults, associated with poor

to their association with clinical outcome. Furthermore, the role of baseline BP and initial BP drop (i.e. within 15 s after standing) in this association is unclear, though these might be determinants of BP recovery [18].

This study in geriatric outpatients addressed the association between BP recovery measures (systolic and diastolic, assessed in subsequent time intervals) and clinical outcome, that is physical and cognitive performance, frailty and number of falls; and the role of baseline BP and initial BP drop in the aforementioned association.

MATERIALS AND METHODS

Study design and setting

Data from two cohorts of patients (Bronovo and COGA) were used. The Bronovo cohort included all patients referred to the geriatric outpatient clinic of the Bronovo hospital (The Hague, the Netherlands) between March 2011 and January 2012. The COGA cohort included all patients referred to the Center of Geriatrics in Amsterdam (COGA) of the VU University Medical Center Amsterdam (Amsterdam, the Netherlands) between January 2014 and December 2015. All patients underwent a comprehensive geriatric assessment (CGA). The studies were performed in accordance with the Declaration of Helsinki and approved by the local medical ethical committee of the VU University Medical Center Amsterdam (COGA cohort) and the institutional review board of the Leiden University Medical Centre (Bronovo cohort).

Patient characteristics

Age, sex, height, weight, medical history, medication, living situation, smoking habits and alcohol consumption were extracted from the medical records. Multimorbidity was defined as two or more of the following diseases: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis.

Blood pressure measurement

A random selection of patients underwent continuous beat-to-beat BP measurements during standing up from supine to standing position. Continuous BP was measured using a finger photoplethysmograph (Nexfin; BMEYE, Amsterdam, the Netherlands). Finger photoplethysmographic continuous BP monitors have been validated using intra-arterial BP measurements both during rest and orthostatic challenges [22–24]. Patients were asked to lie in a supine position for 5 min after which they were asked to stand up and continue standing for 3 min. The last minute of supine resting BP data was used as baseline. Standing up was supported by an automatic lift chair (Vario 570; Fitform B.V. Best, The Netherlands) in the Bronovo cohort. The time instance of standing up was marked in the data.

Blood pressure analysis

All BP signal analyses were performed using MATLAB R2017b (the Mathworks Inc., Natick, Massachusetts, USA). If signals were incomplete (baseline < 30 s or standing time < 150 s) or very noisy on inspection they were

excluded. A 5-s window moving average filter was applied. Signals were split into three epochs based on the transition marker in the data indicating the moment of standing; resting (60 s), transition (7 s) and standing (180 s).

Baseline BP ($BP_{baseline}$) was defined as the mean of the 60-s resting epoch before transition. Initial BP drop ($BP_{initial_drop}$) was defined as baseline minus the minimum BP in the 0 to 15-s interval; minimum BP (BP_{min}) as the lowest BP in this time interval.

BP recovery was evaluated for both SBP and DBP in the following time intervals (t_i) after standing up: 15–30, 30–60, 60–120 and 120–180 s. BP recovery was defined as follows, higher values indicating worse recovery.

$$BP\ recovery_{t_i} = BP_{baseline} - mean(BP_{t_i})$$

Clinical outcome

Physical performance during standing up was assessed using the chair stand test. Patients were asked to stand up from sitting position (knees in 90° flexion) and sit down five times as quickly as possible without the use of their arms or hands [25]. The time in seconds needed to complete this task was used for the analysis.

Cognitive performance was assessed using the Mini Mental State Examination (MMSE; Par Inc, Lutz, Florida, USA) [26]. Subdomains assessed by the MMSE include orientation to time and place, attention, calculation, recall, language, repetition and complex commands.

Frailty was assessed using the Fried frailty criteria, which assess unintentional weight loss, exhaustion, physical inactivity, gait speed and handgrip strength [27]. A patient can be frail on each of these items resulting in a frailty score with range 1–5. Weight loss was defined as a patient-reported loss of more than 3 kg in the previous month or more than 6 kg in the previous 6 months [28]. Exhaustion was assessed using the individual question 'I feel as if I am slowed down' answered with 'very often' or 'nearly all the time' on the Hospital Anxiety and Depression Scale [28,29]. Physically inactive was defined as a patient-reported maximum distance of outdoor walking less than 20 min, only walking indoors or not walking at all [28]. Gait speed was assessed using the 4-m walk test [28]. Handgrip strength was defined as maximal force in kilograms of three performances on each hand, by using hand-held dynamometry (JAMAR hand dynamometer; Sammons Preston, Inc., Bolingbrook, Illinois, USA) [28].

Self-reported number of falls was defined as how many times patients reported to have fallen in the past year.

Statistical analysis

The Statistical Package for the Social Science (IBM SPSS Statistics version 22; IBM Corporation, Chicago, Illinois, USA) were used for statistical analysis. Normally distributed variables were reported using mean and standard deviation (SD); other variables using median and interquartile range (IQR).

The association between BP recovery and physical and cognitive performance frailty was assessed using linear regression analyses with BP recovery as independent variable and physical and cognitive performance as dependent

variables. The association between BP recovery and number of falls was assessed using logistic regression analyses with BP recovery as independent variable and number of falls as dependent variable, dichotomized by the group median. All analyses were adjusted for age and sex in model 1, and additionally adjusted for baseline BP in model 2 and additionally adjusted for initial pressure drop in model 3. All analyses were also performed with standardized (*z*-score) variables, to enable comparison between regression coefficients of the different clinical outcomes.

RESULTS

Table 1 represents the characteristics of the 168 geriatric outpatients (109 and 59 patients from the COGA and Bronovo cohorts, respectively) included in the analyses. The mean age of patients was 81.4 years (SD = 7.0); 55.4% of the patients were female and 83.5% of patients were living at home. Mean SBP and DBP were 139 mmHg (SD = 28.8) and 70.8 mmHg (SD = 13.3), respectively.

Figure 1 shows the associations between BP recovery and physical performance, cognitive performance, frailty and number of falls. The data are provided in eTable 1,

<http://links.lww.com/HJH/B438> and the results from the standardized analysis are provided in eFigure 1, <http://links.lww.com/HJH/B438>. After adjustments for baseline BP and initial BP drop, particularly DBP recovery in the 30 to 60-s interval was associated with physical performance: beta 0.215 [95% confidence interval (CI) 0.05–0.38, *P* = 0.01].

Both SBP and DBP were particularly associated with frailty in the 30 to 60-s interval. Adjustment for both baseline BP and initial BP drop had only minor effect on the strength of these associations. The regression coefficients were 0.013 for SBP (95% CI 0.00–0.02, *P* = 0.02) and 0.028 for DBP (95% CI 0.00–0.05, *P* = 0.02), after full adjustment.

After full adjustment, DBP recovery assessed in the 30 to 60-s interval was particularly associated with the number of falls (odds ratio 1.039, 95% CI 1.00–1.08, *P* = 0.04).

None of the BP recovery measures was associated with cognitive performance.

DISCUSSION

In a cohort of 168 geriatric outpatients, BP recovery after orthostatic hypotension was significantly associated with

TABLE 1. Patient characteristics

Characteristics	All N (%)		Bronovo N (%)		COGA N (%)	Characteristic
Sociodemographic						
Age, years, mean (SD)	168 (100)	81.4 (7.2)	59	80.8 (7.1)	109	81.8 (7.2)
Sex female, <i>n</i> (%)	168 (100)	93 (55.4)	59	33 (56.0)	109	60 (55.0)
Living at home, <i>n</i> (%)	166 (98.8)	137 (82.5)	59	47 (79.7)	107	90 (84.1)
Health characteristics						
Currently smoking, <i>n</i> (%)	162 (96.4)	22 (13.6)	59	9 (15.3)	103	13 (12.6)
Excessive alcohol use, <i>n</i> (%) ^a	131 (78.0)	12 (9.2)	59	6 (10.2)	72	6 (8.3)
Multimorbidity, <i>n</i> (%) ^b	161 (95.8)	70 (43.5)	57	20 (35.1)	104	50 (48.1)
BMI (kg/m ²), mean (SD)	163 (97.0)	25.9 (4.6)	58	26.3 (4.9)	105	25.7 (4.5)
No. of medications, median (IQR)	162 (96.4)	6.0 (4.0–6.0)	58	5.5 (3.8–7.3)	104	7 (4.0–9.0)
Supine resting blood pressure						
Systolic (mmHg), mean (SD)	168 (100)	138.1 (27.6)	59	148.2 (25.8)	109	13.7 (27.0)
Diastolic (mmHg), mean (SD)	168 (100)	70.6 (13.2)	59	72.1 (15.7)	109	68.6 (11.2)
Initial (0–15 s) blood pressure drop						
Systolic (mmHg), mean (SD)	168 (100)	27.6 (23.9)	59	14.2 (19.5)	109	18.3 (22.4)
Diastolic (mmHg), mean (SD)	168 (100)	13.2 (15.4)	59	6.5 (15.2)	109	6.3 (13.8)
Initial orthostatic hypotension, <i>n</i> (%) ^c	168 (100)	61 (36.3)	59	21 (35.6)	109	40 (36.7)
Blood pressure recovery (15–180 s)						
Systolic, 15–30 s, mean (SD)	168 (100)	10.2 (24.3)	59	8.4 (21.7)	109	11.2 (25.6)
Systolic, 30–60 s, mean (SD)	168 (100)	4.4 (23.6)	59	0.7 (21.7)	109	6.4 (26.0)
Systolic, 60–120 s, mean (SD)	168 (100)	–3.5 (26.1)	59	–9.2 (19.8)	109	–0.5 (28.6)
Systolic, 120–180 s, mean (SD)	168 (100)	–6.4 (29.0)	59	–12.2 (22.1)	109	–3.3 (31.8)
Diastolic, 15–30 s, mean (SD)	168 (100)	2.3 (15.7)	59	3.1 (17.8)	109	1.7 (14.5)
Diastolic, 30–60 s, mean (SD)	168 (100)	–1.3 (13.0)	59	–1.8 (14.7)	109	–1.0 (12.0)
Diastolic, 60–120 s, mean (SD)	168 (100)	–4.6 (11.5)	59	–6.0 (11.7)	109	–3.8 (11.4)
Diastolic, 120–180 s, mean (SD)	168 (100)	–5.4 (14.7)	59	–6.3 (11.8)	109	–5.0 (16.0)
Orthostatic hypotension, <i>n</i> (%) ^d	168 (100)	24 (14.3)	59	6 (10.2)	109	18 (16.5)
Clinical outcome						
Chair stand test, <i>s</i> , median (IQR)	133 (79.2)	13.9 (11.3–18.7)	52	14.2 (11.6–19.8)	81	13.7 (10.9–17.8)
MMSE, median (IQR)	159 (94.6)	27.0 (24.0–29.0)	59	27.0 (25.0–29.0)	100	26.0 (23.0–28.0)
Fried frailty score, mean (SD)	130 (77.4)	1.92 (1.3)	59	1.46 (1.2)	71	1.98 (1.2)
Number of falls, median (IQR)	145 (86.3)	1 (0–3)	53	1 (0–2)	92	2 (0–3)

ADL, activities of daily living; BP, blood pressure; IQR, interquartile range; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; OH, prevalence of OH assessed using continuous BP measurements.

^aExcessive alcohol use is defined as more than 14 units per week for women and more than 21 units per week for men.

^bMultimorbidity is defined as at least two diseases of the following: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson disease or rheumatoid(osteo)arthritis.

^cInitial orthostatic hypotension is defined as a SBP drop more than 40 mmHg and/or a DBP drop >20 mmHg within 15 s after standing up.

^dOrthostatic hypotension is defined as a sustained SBP drop more than 20 mmHg and/or a DBP drop more than 10 mmHg occurring within 3 min after standing up.

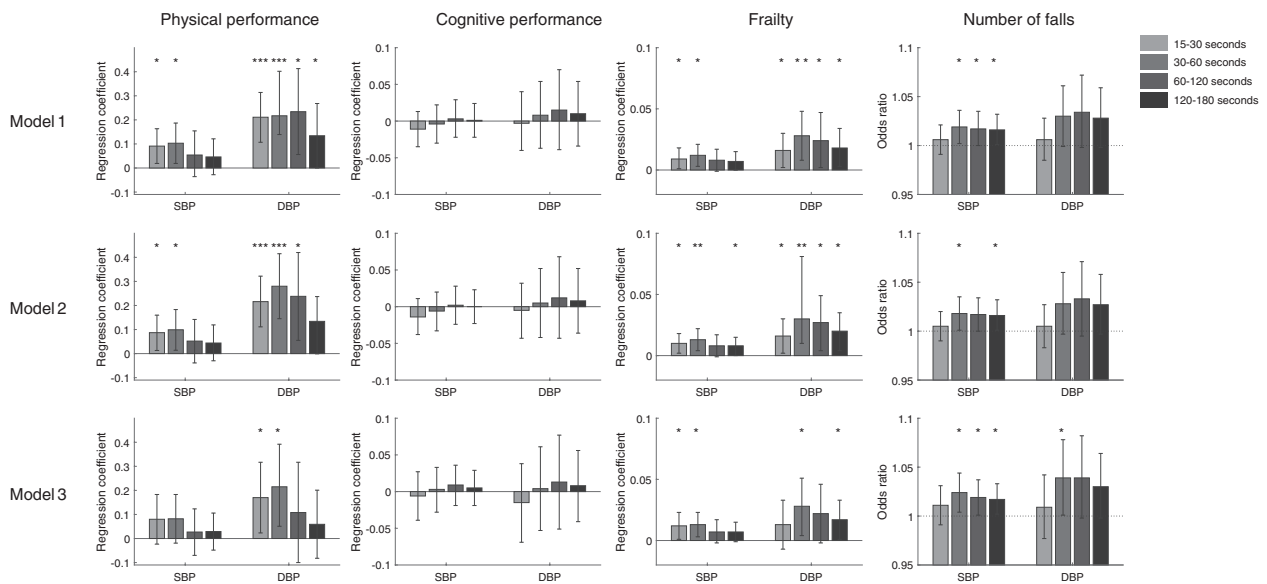


FIGURE 1 Blood pressure recovery and clinical outcome. The bars indicate the regression coefficients/odds ratios of the regression analyses between blood pressure recovery and clinical outcome. Clinical outcome is represented by physical performance ($n = 133$), cognitive performance ($n = 159$), frailty ($n = 130$) and number of falls in the past year ($n = 145$). The error bars indicate the 95% confidence interval. Stars indicate statistical significance, one, two and three stars denoting $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

physical performance, assessed using the chair stand test, frailty according to the Fried criteria and self-reported number of falls, but not with cognitive performance. DBP recovery assessed in the 30 to 60-s interval was particularly associated with clinical outcome. Adjusting the association between BP recovery and clinical outcome for baseline BP and initial BP drop had only minor effect on the strengths of the associations.

The association between BP recovery and number of falls found in the present study as well as the absence of any association between BP recovery and cognitive performance is in line with results from previous studies [15,16,20,21]. However, a recent study reported an association between BP recovery and cognitive decline and mortality in patients with Alzheimer's disease [30]. This may be due to the fact that patients with Alzheimer's disease have increased vulnerability for cognitive decline compared with the population of the present study. The study in patients with Alzheimer's disease also reported DBP recovery assessed at 1 min after postural change to be particularly associated with clinical outcome, which is in line with the findings of the present study [30].

Mechanisms underlying the found associations

The results might indicate that adequate BP recovery after orthostasis may potentially prevent episodes of brain oxygen deficit and thereby improve clinical outcome, as suggested by previous studies reporting hypotensive episodes to be associated with brain white matter hyperintensities and cortical atrophy [7–11,31,32]. However, no conclusions on the causality of the found associations or the involved mechanism can be inferred from the results and orthostatic symptoms are only weakly associated with orthostatic hypotension [33].

Confounding due to degenerative processes causing both worse BP recovery poor clinical outcome might explain part of the results found in the present study. Calf muscle deconditioning may lead to impaired BP recovery, as it has a role in the maintenance of adequate venous return and BP, which may start within seconds after standing up [34,35]. Calf muscle deconditioning may also negatively affect physical performance and increase frailty.

The absence of an association between BP recovery and cognitive performance is remarkable considering the results of a recent meta-analysis, which reported an association between orthostatic hypotension and cognition [4]. These differences may be explained by differences in measurement method (sphygmomanometer BP measurements versus continuous BP measurements) or assessed time interval (initial BP drop within 15 s after standing up versus BP recovery after 15 s after standing up). Furthermore, the relatively high cognitive performance of the overall cohort in the present study may potentially have caused a ceiling effect. Differences may also be partly due to the fact that results reported in the present study were corrected for age, while the results from most studies included in the meta-analysis results were not.

Relative strengths of the associations

The particularly strong association between DBP and clinical outcome may be explained by the large contribution of DBP to cerebral perfusion pressure: cerebral perfusion pressure is defined as mean arterial pressure minus intracranial pressure [36]; mean arterial pressure is a weighted average of systolic (single weight) and diastolic (double weight) BP; in the context of a constant intracranial pressure, changes in DBP have twice as large an effect on cerebral perfusion pressure [37].

Overall, BP recovery was particularly associated with clinical outcome in the 30 to 60-s interval. Explanations remain hypothetical, but could be sought in the brain tolerance for hypoperfusion, that is the time delay between when brain hypoperfusion starts and the first neurobiological consequences. The relatively weaker association in the 120 to 180-s interval with clinical outcome might indicate a compensation mechanism may play a role, though its nature is uncertain. Near-infrared spectroscopy measurements (NIRS) should be performed in future studies to quantify the brain oxygen concentration levels in the different time intervals and relate these to clinical outcome [38–40].

Role of baseline blood pressure and initial blood pressure drop

Adjustment for baseline BP had overall minor effect on the strength of the associations, which may indicate that an individual's physiological regulatory systems (i.e. cerebral autoregulation and baroreflex sensitivity) are adapted to their baseline BP. This would, for example, imply that a DBP recovery value of 30 mmHg would be an equal challenge for individuals with baseline DBP of 100 and 60 mmHg. Adjustment for initial BP drop overall slightly attenuated the strengths of the association between BP recovery and physical performance and frailty, indicating that BP recovery should always be considered in the context of the initial BP drop.

Blood pressure recovery versus blood pressure drop

BP drop and recovery have different mechanisms that cannot be easily disentangled from BP alone. BP drops typically occur due to pooling of blood in the legs caused by gravitational forces within 15 s after standing up [18]. However, venous pooling after standing up may be prolonged [6,41], implying that the BP recovery measures used in the present study may partly reflect this prolonged venous pooling. These BP recovery measures therefore reflect the net BP resulting from BP-lowering gravitational forces and BP-increasing recovery mechanisms such as arterial and venous contraction, heart rate and contractility increase and (calf) muscle activation [34,42–44]. The relative contribution of gravitational forces and the recovery mechanisms to BP varies over time after standing up, and also differs between individuals, complicating the distinction of these mechanisms based on BP measurements alone [6,45]. How recovery mechanisms react to BP drops and how to measure the capacity of the system to recover from BP shifts after postural transitions needs to be further investigated in further studies. These studies should address venous pooling, calf muscle use, heart rate, cardiac contractility and arterial vasoconstriction.

Strengths and limitations

The strength of this study is the systematic assessment of BP recovery measures suggested in the literature with regard to their clinical relevance. Limitations include the cross-sectional design of the study, precluding conclusions about causality, the absence of measurements potentially

indicative for the pathophysiological mechanisms involved (e.g. NIRS), the subjective assessment of the number of falls and the relatively high cognitive performance in the investigated group, which may have caused a ceiling effect in the analyses.

In conclusion, BP recovery was associated with physical performance, frailty and number of falls, but not with cognitive performance. Baseline BP and initial BP drop only played a minor role in this association. The results suggest BP recovery, particularly DBP recovery in the 30 to 60-s interval, to be clinically important. The results further suggest the use of continuous BP measurements for assessment of BP recovery in patients with orthostatic hypotension.

ACKNOWLEDGEMENTS

This study was supported by the perspective grant (Neuro-CIMT, No. 14901) of the AES (Applied and Engineering Sciences), which is part of the Netherlands Organization for Scientific Research (NWO, Utrecht, The Netherlands) and which is partly funded by the Ministry of Economic Affairs.

Furthermore, this study was supported by the European Union's Horizon 2020 research and innovation programme: PreventIT (No 689238) and PANINI (No 675003).

The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

None.

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