Orthostatic hypotension and its association with cerebral small vessel disease in a memory clinic population

1. Julia H.I. Wiersinga*[1, 2]

2. Hanneke F.M. Rhodius-Meester[1, 3,4], MD, PhD

3. Frank J. Wolters [5,12], MD, PhD

4. Marijke C. Trappenburg[1, 6], MD, PhD

5. Afina W. Lemstra[3], MD, PhD

6. Frederik Barkhof [3, 8, 9], MD, PhD

7. Mike J.L. Peters [10], MD, PhD

8. Wiesje M. van der Flier [3, 9, 11], MD, PhD

9. Majon Muller [1, 2], MD, PhD

1. Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Internal Medicine section Geriatrics, Boelelaan 1117, Amsterdam, The Netherlands.
2. Amsterdam Cardiovascular Sciences, Atherosclerosis & Ischemic Syndromes, Amsterdam, The Netherlands.
3. Amsterdam UMC location Vrije Universiteit Amsterdam, Alzheimer Center Amsterdam & Department of Neurology, De Boelelaan 1117, Amsterdam, The Netherlands.
4. Oslo University Hospital, Department of Geriatric Medicine, Ullevål, Oslo, Norway
5. Erasmus Medical Center, Department of Epidemiology, Rotterdam, the Netherlands.
6. Amstelland Hospital, Department of Internal Medicine section Geriatrics, Amstelveen, The Netherlands.
7. Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Radiology, Boelelaan 1117, Amsterdam, The Netherlands.
8. Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, London, UK.
9. Amsterdam Neuroscience, Neurodegeneration, Brain Imaging, Amsterdam, The Netherlands.
10. UMC Utrecht, University of Utrecht, Department of Internal Medicine section Geriatrics, Utrecht, The Netherlands.
11. Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Epidemiology and Biostatistics, Boelelaan 1117, Amsterdam, The Netherlands.
12. Erasmus Medical Center, Departments of Radiology & Nuclear Medicine and Alzheimer Center Erasmus MC, Rotterdam, the Netherlands.

*Correspondence
Julia H.I. Wiersinga
Amsterdam UMC, location VUmc, Internal medicine and Geriatrics
Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
E: j.wiersinga@amsterdamumc.nl
T: +31 20 444 2134

Introduction

Orthostatic hypotension (OH), an impaired blood pressure (BP) response to postural change, has been associated with cognitive decline and dementia (1). OH is defined as a drop in BP of 20mmHg systolic BP (SBP) or 10mmHg diastolic BP (DBP) after standing up (2). This phenomenon is very common in older patients, with a prevalence of approximately 30% (3-5). An earlier study showed that specifically delayed and prolonged OH (DPOH), a drop in BP occurring or remaining after 3 minutes of standing up, is associated with cognitive impairment and progression of cognitive decline (5).

The association between OH and cognitive impairment might be partly driven by the occurrence of cerebral small vessel disease (CSVD). CSVD is a heterogeneous age-related disease and can manifest as white matter hyperintensities (WMHs), lacunes or microbleeds on brain imaging (6). CSVD is common, with prevalence of WMH increasing from about 5% for people aged 50 years to nearly 100% for people aged 90 years (7). The presence of CSVD is strongly associated with vascular cognitive impairment, but CSVD also plays an important role in development and disease burden of other neurodegenerative disorders (8). The pathogenesis of CSVD is not fully elucidated but it is associated with cardiovascular disease and cardiovascular risk factors such as high BP, diabetes, and hypercholesterolemia (9, 10). Hypoperfusion of the brain through oxidative stress might also play an important role in the etiology of CSVD (11, 12). As such OH might cause CSVD through recurrent transient episodes of cerebral hypoperfusion after standing up (13, 14). Yet, current knowledge on the relation between OH and CSVD is inconclusive, with clinically relevant associations observed in older community dwelling individuals, but not in patients with dementia (15-17). However, these studies did not account for supine BP, or the duration and magnitude of the BP drop, which could be indicators for the degree of cerebral hypoperfusion.

Therefore, we hypothesized that specifically DPOH would be more strongly associated with CSVD than EOH, due to longer periods of hypoperfusion and an increased magnitude of drop in BP would lead to more cerebral hypoperfusion as well and therewith to more CVSD. In this study, we investigated the association between OH and CSVD in a memory clinic setting, with attention to the duration of OH and the magnitude of the BP drop.

Methods

Design and population

This observational cross-sectional cohort study included 3971 consecutive outpatients with cognitive complaints from the Amsterdam Ageing Cohort (AAC study; n=1066) and Amsterdam Dementia Cohort (ADC; n=2905). Both AAC and ADC are longitudinal cohort studies in patients visiting outpatient geriatric/memory clinic at the Amsterdam University Medical Center, location VUmc. (18, 19). All patients underwent a standardized clinical assessment including neuropsychological and geriatric screening, BP measurements and MRI or CT Imaging of the brain. Clinical diagnoses were made by a multidisciplinary team according to international guidelines. For this study, we included all patients who were diagnosed with either 'subjective cognitive complaints' (including psychiatric disorders), 'mild cognitive impairment (MCI), or 'dementia' (including Alzheimer's Disease, Dementia with Lewy Bodies, Vascular Dementia, Frontotemporal Dementia, mixed dementia and undetermined type) (19-23).

The local Medical Ethical committee approved the study protocols and all patients provided written informed consent.

Demographics and clinical characteristics

Descriptive characteristics were assessed during the visit at the clinic and included age, sex, alcohol use (use/day) and smoking (never smoked versus current or history of smoking). History was extracted from the electronic medical file and status from the outpatient clinic visit. We defined (yes/no) history of cardiovascular disease (myocardial infarction (MI), angina pectoris (AP), peripheral artery disease (PAD), cerebrovascular accident/transient ischemic attack (CVA/TIA, both ischemic and hemorrhagic), heart failure (HF) and atrial fibrillation (AF)), presence of cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes), presence of Parkinson's disease or a diagnosis of Lewy Body disease, and use of OH-inducing medication (antihypertensive drugs, long-acting nitrates, alpha-blockers, antidepressants, or antipsychotic drugs, see supplemental file for full list). And we recorded global cognitive function using the mini-mental state exam (MMSE) (24)and Montreal Cognitive Assessment (MoCA) (25).

Orthostatic hypotension

BP was measured by a doctor's assistant with a Dinamap© automated BP monitor at baseline in supine position after lying down for at least 3 minutes followed by a measurement at 1 and 3 minutes after standing up. Supine SBP, DBP and heart rate were collected. OH was defined as a drop in SBP of at least 20mmHg and/or a DBPof at least 10mmHg (2). This was further divided in to early and and/or prolonged OH. Early OH was defined as OH only at 1 minute of standing up, delayed as

OH only at 3 minutes of standing up and prolonged at both 1 and 3 minutes. Delayed and prolonged OH were combined. For the baseline analysis, the population was divided into three groups: no OH, early OH (EOH) and delayed or prolonged (DPOH).

Furthermore, we assessed the magnitude of drop in SBP and DBP and divided this into steps of respectively 10mmHg and 5mmHg. Lastly, the heart rate response (HRR) after standing up (difference in supine and standing heart rate), both at 1 and 3 minutes, was determined.

Cerebral Small Vessel Disease

All patients underwent brain imaging during their first visit with either CT (n=389) or MRI (n=3584). The scans were reviewed and scored by two trained specialists and supervised by a clinical radiologist according to the local dementia protocol. White matter hyperintensities were scored on either CT or FLAIR/T2 sequence on MRI using the Fazekas scale (0–3) (26). The number of lacunes and (only on MRI) microbleeds (on susceptibility-weighted imaging) were counted. Small vessel disease was defined in three ways: as a Fazekas score of ≥2 yes/no, presence of 1 or more lacunes yes/no, or presence of ≥3 microbleeds yes/no, and these are separately presented (27-29). In addition, cortical infarcts and macrobleeds were assessed using the same local dementia protocol.

Statistical analysis

Baseline characteristics were calculated for the total population and according the OH subgroups (no OH, EOH, DPOH). Continuous and dichotomized variables were compared using parametric and nonparametric tests where appropriate. Least significant differences were used for post-hoc testing for significant findings. Statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Logistic regression analyses were used to investigate the association between OH, divided into no OH, EOH and DPOH (with no OH as reference group) and the presence of MRI markers of cerebral small vessel disease yes/no in three separate analyses (Fazekas score ≥2, presence of lacunes and presence of ≥3 microbleeds). Analyses were adjusted for age and sex in model 1 and, additionally for presence of OH-inducing drugs and MMSE-score presence of cardiovascular disease and diabetes (model 2), and additionally for supine SBP (model 3).

Next, logistic regression analyses were used to determine the association between the magnitude of drop in SBP and DBP in steps of respectively 10mmHg and 5 mmHg and markers of CSVD (model 1-3). A drop of less than 10 mmHg or an increase was used as reference value for SBP and likewise with 5 mmHg for DBP.

Finally, sensitivity analyses were performed 1) stratifying the population for patients Parkinson's disease and Lewy Body Disease ,and 2) excluding patients with cortical infarct on their brain imaging to investigate if our results were driven by these groups, due to the strong associations of these conditions with OH. Furthermore, we performed additional sensitivity analyses 3) by excluding CT scans, stratifying for 4) cohort (AAC/ADC) and 5) Age <70/>=70.

Results

Baseline

The mean (SD, range) age of the total population (N=3971) was 67.5 (+/- 10.8) years and 1784 (44.9%) were women. Of the total population, N=376 (9%) had EOH, and N= 722 (18%) had DPOH (table 1).

Compared to patients without OH, patients with EOH or DPOH were older, sex was similar between OH groups. MoCA scores were lower in patients with DPOH, MMSE scores were similar. Cognitive diagnosis was similar between groups.

Patients with OH more likely to have a history of atrial fibrillation, CVA/TIA and peripheral arterial disease and were prescribed OH-inducing drugs (antihypertensive drugs, antipsychotic drugs and alpha-blockers) more often, and had higher supine SBP levels. Furthermore, compared to patients without OH patients with DPOH had higher supine DBP levels and lower MoCA scores (Table 1).

Orthostatic hypotension and cerebral small vessel disease

In the overall population, 1214 (31%) patients had moderate to severe WMH (Fazekas ≥2), 502(13%) had ≥1 lacunes, and 278 (8%) had ≥3 microbleeds. These markers of CSVD were more prevalent in patients with EOH (WMH and microbleeds) and DPOH (all imaging markers), compared to patients without OH (Table 2).

Logistic regression analysis, adjusting for age and sex, showed that only DPOH, but not EOH, was significantly associated with and increased risk of having WMH and lacunes; ORs (95%CI) were respectively 1.25 (1.03-1.51) and 1.33 (1.06-1.68) (Table 3). EOH nor DPOH were significantly associated with an increased risk of microbleeds (1.21 (0.89-1.65)) (Table 3). Additional adjustments for OH-inducing drugs, history of CVD, history of diabetes, and MMSE-score (model 2), did not change the effect estimates. After additional adjustment for supine SBP, all estimates strongly attenuated and were no longer statistically significant (model 3).

Drop in blood pressure

Logistic regression analyses (figure 1-3a) associating the drop in BP after standing with risk of having CSVD showed that an increased drop in SBP is associated with an increased risk of having WMH and microbleeds (p-value for trend respectively 0.05 and 0.06), but not with an increased risk of having lacunes (p-value for trend 0.27). After additional adjustment for SBP all associations disappeared (fig 1-3b). A drop in DBP was not associated with CSVD (data not shown).

Sensitivity analyses

Additional analyses (model 2) by 1) excluding patients with Parkinson's disease and Lewy Body Disease (n=142), 2) excluding patients with large cortical infarcts on brain imaging (n=204) and 3) excluding patients with CT scans did not change the effect estimates (data not shown). Stratified analyses in patients with Parkinson's disease and Lewy Body Disease did not show a significant association.

Stratified analyses (model 1) by cohort showed that the effect sizes differed slightly between the ADC and AAC population, however, not significant in interaction models. All effect sizes diminished in model 2 due. Stratification for age group (<70/>=70 yrs) showed that the association between DPOH and both WMH and lacunes (model 2) was more pronounced in patients older than 70 years (data not shown), but with overlapping confidence intervals.

Discussion

OH, and specifically DPOH, is common in this large cohort of memory clinic patients. Particularly patients with DPOH have a higher burden of CSVD. However, this association was largely due to supine SBP. These findings illustrate that the association between OH and CSVD is driven by the confounding effect of supine SBP.

Earlier studies yielded conflicting results regarding the association between OH and CSVD. Some studies found no relation between OH and CSVD (30, 31), while others did (15, 32). These conflicting results could be due to inconsistent OH measurements, e.g. not taking into account duration and magnitude of the blood pressure drop after standing up, and differences in definition of CSVD. Furthermore, adjustment for confounding factors were inconsistent. Our results are in line with earlier studies showing that presence of OH after 3 minute standing, when compared to 1 minute or earlier, was related to a significant increased risk of having WMH (32) and that larger drop in SBP was associated with CSVD (33). However, none of these earlier studies adjusted for supine SBP.

There are several possible mechanisms that can explain our findings. In our study supine SBP is the main driver for the association between OH and CSVD. Both OH and the occurrence of CSVD are strongly associated with uncontrolled hypertension and high SBP (6, 34, 35). Therefore, the OH - CVSD association might be the consequence of high SBP pressure rather than OH (32, 36, 37). This finding poses several questions and possible consequences. It could be hypothesized that supine SBP enhances the risk of cerebral small vessel disease through increase in duration and magnitude of the orthostatic blood pressure drop. The last, and most probable, explanation is that not OH, but increased supine SBP drives the association. Our results suggest that not hypoperfusion but high SBP is leading to the development CSVD (38, 39).

Clinical relevance

So what is the additional value of this study for our daily clinical practice? Treatment of OH is complex and antihypertensive medications are commonly deprescribed in patients with OH. However, evidence does not support the routine deprescription in asymptomatic patients with hypertension and OH. By contrast, previous studies report that the OH prevalence is higher in adults with uncontrolled rather than controlled hypertension (19% versus 5%; $p < 0.001$ (40)) and that aggressive antihypertensive treatment reduce OH risk (41). Moreover, BP lowering treatment in randomized controlled trials did not result in reduction of cerebral perfusion (42). This is in line with the SPRINT trial, in which they showed that intensive blood pressure control (SBP target <120 mmHg) did not increased the risk of OH and was longitudinally associated with a significantly smaller increase in cerebral white matter lesion volume, and should be considered in older patients (43).

Intensifying antihypertensive medication might feel counterintuitive if one wants to prevent hypotension and (detrimental effects of) cerebral hypoperfusion. However, if an increased SBP increases the risk of orthostatic hypotension and cerebral small vessel disease, adequate blood pressure management is necessary to reduce these risks (44). Our data support the need for further research on optimal blood pressure management in patients with OH and CSVD.

Although this study is one of the first to study the relationship between OH and CSVD in such a large well phenotyped cohort of memory clinic patients, there are certain limitations that must be addressed. First, a major limitation of current research was its cross-sectional design, which limits conclusion on the direction of the association of OH and CSVD. Secondly, our OH measurements were limited: we did not have continuous BP measurements or information on BP variability after 3 minutes. This would have given even more insight into how duration and magnitude of BP drop was associated with cerebral small vessel disease. Nonetheless, we used a widely acceptable and clinically feasible measurement of BP variability after postural change, and were still able to differentiate between EOH and DPOH and shown the importance of DPOH.

In conclusion, we found that in memory clinic patients we found that the relation between OH and CSVD was driven by the confounding effect of supine BP.

Acknowledgments

We acknowledge the support from the Netherlands CardioVascular Research Initiative: the HBCx Dutch Heart Foundation (CVON 2018-28 & 2012-06 Heart Brain Connection), Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Research of the Alzheimer's Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. The Vrije Universiteit Medical Center Alzheimer Center is supported by the Stichting Alzheimer Nederland and Stichting Vrije Universiteit Medical Center Fonds. The collaboration project Dementia diagnostics using Artificial Intelligence (DAILY; project number LSHM19123-HSGF) is co-funded by the public–private partnership allowance made available by Health-Holland, Top Sector Life Sciences and Health, to stimulate public–private partnerships and Combinostics. The chair of WF is supported by the Pasman Stichting. WF and HR are recipients of ABOARD, which is a public–private partnership receiving funding from ZonMW (number 73305095007) and Health-Holland, Top Sector Life Sciences and Health (public–private partnership allowance; number LSHM20106). WF is recipient of the EU Joint Programme - Neurodegenerative Disease Research (JPND) project EURO-FINGERS (ZonMW-Memorabel #733051102) which is supported through the following funding organizations under the aegis of Joint Programme-Neurodegenerative Disease: Finland, Academy of Finland; Germany, Federal Ministry of Education and Research; Spain, National Institute of Health Carlos III; Luxemburg, National Research Fund; Hungary, National Research, Development and Innovation Office; The Netherlands, Netherlands Organisation for Health Research and Development; Sweden, Swedish Research Council (grant agreement INTER/JPND/19/BM/14012609). HR is recipient of the Memorabel Dementia Fellowship 2021 (ZonMw projectnumber 10510022110004) and Alzheimer Nederland InterACT grant (projectnumber WE.08-2022-06).

We also thank all the students and nurses working at memory outpatient clinic of Amsterdam UMC and Vrije Universiteit Medical Alzheimer Center.

Sources of Funding

None.

Declaration of Interest

HRM performs contract research for Combinostics; all funding is paid to her institution.

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