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ORIGINAL ARTICLE

Orthostatic blood pressure recovery in older males using alpha-blockers for lower urinary tract symptoms, an explorative study in a urology outpatient clinic

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Abstract

What is known and objective: Alpha-blockers have been associated with orthostatic hypotension (OH). We aimed to assess the prevalence of OH measured with beat-to-beat blood pressure monitoring in older male outpatients who used alpha-blockers for lower urinary tract symptoms (LUTS). In addition, we investigated associations of OH with duration of alpha-blocker use, concomitant medication use and comorbidity.

Methods: Cross-sectional explorative study in a urology outpatient clinic. Older white males ≥65 years using alpha-blockers for LUTS were included. Blood pressure responses to standing up from supine were recorded using a validated beat-to-beat blood pressure device (Finapres). Prevalence rates were derived from the beat-to-beat data to include OH measured between 60–110 s (OH), impaired recovery OH at 40 s (OH[40]), initial OH (IOH) and normal orthostatic response. Subgroups were defined based on duration of alpha-blocker use, polypharmacy, and Charlson comorbidity index (CCI), to obtain relative risks.

Results and discussion: Sixty-five patients were included. Median age was 75 years (range 65–92). The prevalence of OH was 7.7% ($n = 5$). The prevalence of OH(40) was 16.9% ($n = 11$) and of IOH 38.5% ($n = 25$). Thirty-six patients (55.4%) had a normal orthostatic response. The relative risk of OH for the subgroup using ≥ 10 medications ($n = 13$) was 6.0 (95%CI 1.1–32.3). For the subgroup with multimorbidity (CCI ≥3, $n = 11$) this was 7.4 (95%CI 1.4–39.0). Recent initiation of alpha-blocker use (<3 months) did not increase OH risk (RR 0.6 [95%CI 0.1–5.1]).

What is new and conclusion: The overall prevalence of OH was low and comparable to age-matched population prevalence, suggesting that the relative contribution of alpha-blockers to OH was small. However, OH risk significantly increased in patients with multimorbidity or polypharmacy. For these patients, the benefits of starting alpha-blockers for LUTS should be weighed against the increased risk of OH.

KEYWORDS
LUTS, multimorbidity, orthostatic hypotension, polypharmacy, side effect

1 | WHAT IS KNOWN AND OBJECTIVE

Alpha-1 adrenergic receptor antagonists (alpha-blockers) are considered the first line of treatment for male patients with lower urinary tract symptoms (LUTS).[1] LUTS caused by benign prostatic hyperplasia (BPH) is common and its prevalence increases with age.[2,3] Eighty-eight percent of males over 80 years of age have histologically confirmed BPH, of whom 25%–50% will have symptoms.[2,4]

Alpha-blockers were originally developed for the treatment of hypertension, but when their local effects on prostate tissue became clear they were soon applied to relieve symptoms of LUTS/BPH.[5] Common side-effects are understandably related to their antihypertensive properties and include asthenia, dizziness and (orthostatic) hypotension.[1] Modern alpha-blockers to treat LUTS have been developed to be more alpha-1a receptor "uroselective", with the goal of increasing tolerability.[6] However, a potential effect on postural blood pressure regulation remains as alpha-1a receptors also play an important role in vasoconstriction of femoral and cutaneous resistance arteries.[7,8]

Orthostatic hypotension (OH) is an exaggerated drop of blood pressure and recovery deficit thereof that occurs after standing up from a seated or supine position. Older patients have an increased risk of OH due to a multitude of age-associated physiological changes as well as an increased prevalence of comorbid conditions, such as type 2 diabetes and hypertension, and concomitant medication use, such as diuretics, benzodiazepines and antidepressants.[9,10] Falls and fractures have been associated with OH, although the direct association between alpha-blockers medication and falls and fractures is still contested.[11–13]

Several studies have investigated (postural) blood pressure changes related to alpha-blockers, but those studies generally applied strict selection criteria resulting in the inclusion of relatively healthy groups of patients.[14–19] Additionally, little information was reported on how and when the orthostatic hypotension measurements were carried out. A beat-to-beat blood pressure monitor allows for continuous measurements of blood pressure (BP) and is therefore more sensitive to changes in BP. This method can identify several recognized subtypes of OH, such as initial orthostatic hypotension (IOH) and impaired recovery orthostatic hypotension (OH(40)).[20]

The purpose of this study was to determine the prevalence of OH using these specified beat-to-beat definitions in older urologic outpatients who were prescribed alpha-blockers for LUTS and to investigate associations with duration and type of alpha-blocker use, concomitant medication use and comorbidity.

2 | METHODS

2.1 | Setting and participants

This cross-sectional explorative study was carried out at the urology outpatient clinic of a large teaching hospital in the Netherlands. The study protocol was approved by the local research ethics committee and all patients provided informed consent prior to inclusion. The study adhered to the provisions of the Declaration of Helsinki. Male outpatients ≥65 years using alpha-blockers for LUTS were eligible to participate. Patients who visited the clinic between January and April 2018 were asked to participate by their urologists. When patients were willing to participate, the researcher checked for exclusion criteria and asked informed consent. Exclusion criteria were: no compliance for their alpha-blockers in the previous 24 h, inability to stand for 3 min, coexisting disorders that would impair a reliable beat-to-beat BP measurement (e.g., active systemic inflammatory disease or arrhythmias such as atrial fibrillation). All human subjects provided written informed consent with guarantees of confidentiality.

2.2 | Data collection

Baseline characteristics, type and start date of the alpha-blocker, number of falls in the previous 6 months, frequency of postural complaints experienced in daily life (Likert-5 scale), current medication and medical history were obtained. Starting date of the alpha-blockers was retrieved from the electronic patient file if they had recently (<6 months) been started, or as recalled by the patient in case they had been started over 6 months ago. Other medication use was retrieved from patients' current medication overview, or from their electronic patient file and was verified with the patient. Medical history as recalled by patient and verified using the electronic patient file was classified using the updated Charlson comorbidity index (CCI).[21]

2.3 | Orthostatic BP measurement

Measurements were done at least one hour after the last meal. OH measurements were performed using the Finometer PRO (Finapres Medical Systems, Amsterdam, Netherlands), a dynamic beat-to-beat noninvasive blood pressure monitor that uses digital artery volume-clamp photoplethysmography. Patients rested for a period of at least 10 min in supine position prior to standing up. They were requested to stand up quickly (within 5 seconds) and to remain standing for 3 min. Patients were asked to report any sensations or complaints they experienced directly after standing up and every minute thereafter. The Finometer was started proceeding the resting period. After 2 min of supine resting a return to flow calibration was performed using upper arm cuff inflation. A marker was recorded 2 min before standing. The Finometer's automatic calibration protocol (Physiocal) was switched off at this time to ensure an uninterrupted BP recording. This approach is similar to the orthostatic BP measurement as reported in the Irish longitudinal study on ageing (TILDA), a large cohort study assessing the prevalence of OH subtypes amongst community-dwelling older persons using a similar beat-to-beat BP monitor.[20]

2.4 | Orthostatic BP analysis

Baseline values for SBP and DBP were derived from the mean values between 120 and 60 s prior to standing. Beat-to-beat data was analyzed using Beatscope software version 1.1a (TNO TPD Biomedical Instrumentation, Amsterdam, the Netherlands). Data were manually screened for usability (signal quality and artefacts) and preprocessed using the marker placed during the measurement as a reference point. Time point 0 (moment of getting up) was identified approximately 2 min after the marker by the initial rise in BP related to orthosympathetic muscle activation, followed by a drop in BP. Baseline SBP and DBP were calculated and beat-to-beat data from time point 0 to 190 s was exported with 5 second averaging for OH, sustained OH and OH(40) analysis and 2 s averaging for IOH analysis (see definitions below). Data were imported into Libreoffice Calc (version 6.0.1, The Document Foundation, Berlin, Germany) and further analyzed using custom written macros.

2.5 | Outcomes and definitions

We chose to follow the definitions for the different subtypes of OH that can be detected using beat-to-beat BP measurements as previously established in the TILDA study.[20] This allowed us to compare our data to their large normative dataset and compare age-specific prevalence rates of OH and its subtypes.

OH was defined as sustained failure of systolic blood pressure (SBP) or diastolic blood pressure (DBP) to stabilize to within 20 mmHg SBP and/or 10 mmHg DBP of supine levels from 60–110 s after active standing. Impaired recovery orthostatic hypotension (OH(40)) was defined as a failure of SBP or DBP to stabilize to within 20 mmHg SBP and/or 10 mmHg DBP of supine levels at 40 s after standing.

OH(40) is a subtype of OH that has been identified as a predictor of falls and mortality.[11,22] Initial orthostatic hypotension (IOH), a subtype that is also recognized in the consensus statement on the definition of orthostatic hypotension,[9] was defined as a transient BP decrease of more than 40 mmHg SBP and/or > 20 mmHg DBP within 15 s of standing. Despite being accompanied by symptoms in some cases, there is debate over the clinical relevance of IOH, which has been suggested could be an exaggerated physiological response influenced by the mechanical act of standing up.[11,23]

Sustained OH was defined as sustained failure of SBP or DBP to stabilize to within 20 mmHg SBP and/or 10 mmHg DBP of supine levels from 60–180 s after active standing.[9] Sustained OH is a more pronounced form of OH and is based on the original definition designed for regular BP monitors, but applied to beat-to-beat measurements.

Our main outcomes were the prevalence of OH and OH(40). OH has been previously associated with alpha-blocker usage and for OH(40) at least a theoretical relationship with (nonselective) alpha-1 blockade exists.[24] Secondary outcomes were prevalence of IOH and sustained OH, and the relative risk of OH (vs. not OH) associated with duration and type of alpha-blocker use, concomitant medication use, and comorbidity. Relative risks were also calculated for OH(40) (vs. not OH(40)) and for the combined group of OH or any subtype (vs. normal orthostatic response).

2.6 | Statistical analysis

The prevalence for each subtype of OH was calculated. Next, patients were divided into subgroups according to their age (65–74 years old vs. ≥75 years old), the duration of alpha-blocker usage (<3 months vs. ≥3 months), type of alpha-blocker used (silodosin vs. tamsulosin/

TABLE 1 Baseline characteristics

	Total (n = 65)	OH or any subtype (n = 29)	Normal orthostatic response (n = 36)
Age *median (range)*	75 (65–92) years	76 (65–87)	74 (65–92)
BMI *mean (SD)*, kg/m^2	26.0 (3.4)	24.8 (2.9)	27.0 (3.5)
Duration of alpha-blocker use *median (range)*, months	13 (1–182)	9 (1–134)	18 (1–182)
Alpha-blocker used *Tamsulosin Silodosin Alfuzosin*	55 (84.6%) 8 (12.3%) 2 (3.1%)	26 (89.7%) 3 (10.3%) 0	29 (80.6%) 5 (13.9%) 2 (5.6%)
Number of medications *median (range)*	5 (1–21)	6 (1–21)	5 (1–16)
Charlson comorbidity index *median (range)*	1 (0–6)	0 (0–6)	1 (0–5)
Baseline systolic blood pressure *mean (SD)*, mmHg	141 (22)	151 (20)	134 (20)
Baseline diastolic blood pressure *mean (SD)*, mmHg	72 (10)	74 (11)	71 (8)
Use of any antihypertensives[a]	31 (47.7%)	12 (41.4%)	19 (52.8%)
Frequency of postural complaints in daily life *Never or rarely Sometimes or more frequently*	42 (64.6%) 23 (35.4%)	15 (51.7%) 14 (48.3%)	27 (75.0%) 9 (25.0%)
Falls in previous 6 months	12 (18.5%)	4 (13.8%)	8 (22.2%)

Abbreviations: BMI, body mass index; OH, orthostatic hypotension; SD, standard deviation.
[a]The following drug classes were classified as antihypertensives: ACE-inhibitors, angiotensin receptor blockers, beta blockers, calcium antagonists, diuretics, and long-acting nitrates.

alfuzosin), number of medications (<10 vs. ≥10), comorbidity (CCI <3 vs. ≥3). For each of the groups a relative risk (RR) and 95% confidence interval (CI) was calculated for OH, OH(40) and OH or any subtype combined. Statistical analysis and data management was done with SPSS (version 20, IBM, Armonk, New York, United States of America).

3 | RESULTS AND DISCUSSION

3.1 | Participant characteristics

Seventy-two patients were included in the study. Data of seven measurements were excluded for reasons of beat-to-beat quality and previously nondisclosed and undetected arrhythmia. Table 1 provides an overview of patient characteristics. Median age was 75 years (range 65–92), median CCI was 1 (range 0–6). Eighty five percent of patients used tamsulosin and 65% never or rarely experienced postural complaints in daily life.

3.2 | Prevalence of OH and its subtypes

Five (7.7%) patients met criteria for OH, 11 (16.9%) met criteria for OH(40), 25 (38.5%) met criteria for IOH and 2 (3.1%) met criteria for

TABLE 2   Prevalence of orthostatic hypotension subtypes

	Prevalence	Symptoms during measurement
OH	5 (7.7%)	2 (40%)
OH(40)	11 (16.9%)	5 (45.5%)
IOH	25 (38.5%)	14 (56%)
Sustained OH	2 (3.1%)	2 (100%)
Normal orthostatic response	36 (55.4%)	14 (38.9%)

Abbreviations: IOH, initial orthostatic hypotension; OH, orthostatic hypotension; OH(40), impaired recovery orthostatic hypotension.

sustained OH. Thirty-six (55.4%) had a normal orthostatic response (Table 2). Symptoms were reported in 2 (40%) patients with OH, 5 (45.5%) with OH(40), 14 (56%) with IOH and both patients with sustained OH, whereas 14 (38.9%) patients with a normal orthostatic response expressed symptoms.

All 5 patients meeting the criteria for OH also met the criteria for OH(40) and 2 of them also met criteria for IOH. Seven patients met criteria for both IOH and OH(40) (but not OH). Both patients with sustained OH automatically met criteria for OH.

3.3 | Association of OH with other factors

Patients were divided into subgroups to investigate associations with OH, OH(40), and OH or any subtype combined. Relative risks and 95% CI for OH (vs. not OH) and for OH or any subtype (vs. normal orthostatic response) are summarized in Table 3. The relative risk of OH was higher in patients using 10 or more medications (RR 6.0) and in patients with a CCI of 3 or higher (RR 7.3). It should be noted that the patients with a high CCI also used a larger number of medications. There was no association between OH and duration or type of alpha-blocker use. For OH(40), results in a similar direction were observed, although not statistically significant (data not shown).There was no association between presence of OH or any subtype and duration or type of alpha-blocker use, polypharmacy or comorbidity, compared to patients with normal orthostatic response.

3.4 | Discussion

This explorative cross-sectional study provides a comprehensive evaluation of the prevalence of OH and its subtypes, measured with a beat-to-beat BP monitor, in patients using alpha-blockers for LUTS.

We found a prevalence of 7.7% for OH. Overall, this prevalence is comparable to age-matched prevalences observed in the general

TABLE 3   Prevalence and relative risk of orthostatic hypotension (OH) and OH plus subtypes in different subgroups

	Prevalence of OH	Relative risk (95% CI)	Prevalence of OH or any OH subtype	Relative risk (95% CI)
Duration of alpha-blocker use				
≥3 months	8.7% (4/46)		45.7% (21/46)	
<3 months	5.3% (1/19)	0.6 (0.1–5.1)	42.1% (8/19)	0.9 (0.5–1.7)
Type of alpha-blocker				
Silodosin	12.5% (1/8)		37.5% (3/8)	
Tamsulosin/ Alfuzosin	7% (4/57)	0.6 (0.1–4.4)	45.6% (26/57)	1.2 (0.5–3.1)
Number of medications				
<10	3.8% (2/52)		42.3% (22/52)	
≥10	23.1% (3/13)	6.0 (1.1–32.3)*	53.8% (7/13)	1.3 (0.7–2.3)
Charlson comorbidity index				
<3	3.7% (2/54)		42.6% (23/54)	
≥3	27.3% (3/11)	7.4 (1.4–39.0)*	54.5% (6/11)	1.3 (0.7–2.4)

Note: *p < 0.05.

population. The TILDA study found a prevalence of OH in men of 5.8%, 7.9%, and 18.9% for the age-groups 60–69 years, 70–79 years, and 80+ years, respectively.[20] For OH(40), a classification of OH that has been associated with increased risk of falls, we found a prevalence of 16.9%, which is also comparable to the general population prevalence of 15.5%, 24.7% and 43.4% in men aged 60–69 years, 70–79 years, and 80+ years, respectively.[20]

However, in our a priori defined subgroups with polypharmacy and comorbidity, we observed a more than 6-fold increased risk of OH. It is conceivable that in these patients the physiological compensatory mechanisms for orthostatic stress are already hampered by disease or medication, and the alpha-blocker is the straw that breaks the camel's back. We found no clear relationship between treatment duration and OH, in line with an interventional study of tamsulosin.[17] Specifically, we found no indication that recent start led to higher OH prevalence. This may be confounded by low treatment adherence in men with LUTS: a "first" dose phenomenon could temporarily occur again after a period of prolonged treatment discontinuation.[25]

When comparing patients with any subtype of OH (i.e., OH, OH(40), IOH and sustained OH) as a group to the patients with normal orthostatic response, we found no effect of polypharmacy or comorbidity. This suggests that the different subtypes of OH are in fact different pathophysiological entities elicited by different factors, and that some or all subtypes, apart from OH, have no association with comorbidity of polypharmacy. The subgroup sizes however are too small for definitive conclusions.

Strengths of this study include the fact that we used a beat-to-beat BP monitor to assess patients for OH, allowing us to detect previously underreported subtypes of OH aside from Consensus definitions. A single OH measurement may lead to underdetection of OH due to the poor reproducibility of OH measurements. However, this was mitigated by our more sensitive continuous blood pressure recordings. Our broad in- and exclusion criteria guarantee a representative selection of older urologic outpatients. We were, however, dependent on the urologists for recruitment, and have no way of knowing how many potentially eligible patients were not approached. It is possible that the patients willing to participate were a selection of fitter patients. We think that our finding that polypharmacy and comorbidity increased the risk of OH would not have been different, but rather more pronounced, had more frail patients participated.

Further limitations of this study are the relatively small sample size, limiting our ability to perform subgroup analyzes. The comparisons between the types of alpha-blocker used were limited by the large proportion of patients being prescribed tamsulosin. Our study lacks a control group that does not use alpha-blockers, however, the standardized measurement protocol allowed direct comparison to a large prevalence study in the general population.[20]

4 | WHAT IS NEW AND CONCLUSION

We found that the overall prevalence of OH and its subtypes was comparable to the prevalence in the age-matched general population.

This suggests that as a single factor, alpha-blockers do not increase the risk of OH in men with LUTS. However, in interaction with comorbidity and polypharmacy, we observed a 6-fold higher prevalence of OH. For these patients, the benefits of starting or continuing alpha-blockers for LUTS should be weighed against the increased risk of OH.

CONFLICT OF INTEREST

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations to the subject matter or materials discussed in the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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