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The assessment of the relationship between anticholinergic burden and short-term blood pressure variability

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Abstract

Background This study aimed to investigate the relationship between short-term blood pressure variability (BPV) and anticholinergic burden (ACB) in adults with hypertension.

Methods This study included 238 hypertensive patients aged 50 and older who underwent ambulatory blood pressure monitoring. The medications used by the patients were recorded, and the ACB of each medication was calculated using the ACB Scale. The BPV was assessed based on 24-hour ambulatory blood pressure measurements using three methods: standard deviation (SD), coefficient of variation of the standard deviation (SD-CoV), and weighted standard deviation (wSD), with evaluations conducted for both day-time and night-time periods.

Results A total of 139 patients (58.40%) had no ACB score, 64 (26.89%) had an ACB score of 1, and 35 (14.71%) had an ACB score of 2 or higher. ACB scores were significantly higher among patients with heart disease, and ACB tended to increase with age. However, no statistically significant relationship was found between ACB and mean blood pressure, nocturnal blood pressure dips, or any parameters of short-term BPV including Sd, SD-CoV and wSD.

Conclusion No significant association was found between ACB and short-term BPV. To the best of our knowledge, this is the first study to investigate this relationship, which may inspire further research.

Keywords Anticholinergic burden, Hypertension, Ambulatory blood pressure measurement, Blood pressure variability

Background

Mean clinical blood pressure values are traditionally considered the gold standard for the diagnosis and treatment of hypertension in patients with hypertension; however, recent studies conducted with hypertensive individuals have demonstrated that the evaluation and quantification of blood pressure variability (BPV), in addition to standard blood pressure values have both physiopathological and prognostic significance [1, 2]. There is strong evidence suggesting that increased BPV is independently associated with a higher risk of target organ damage, cardiovascular events, and death [1, 3]. There are also

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studies showed diastolic hypotension is a major problem which is related to increased mortality and hospitalizations in older adults under antihypertensive treatment [4, 5].BPV is examined in three groups: very short, short, and long-term BPV [6]. Very short-term BPV refers to fluctuations in blood pressure between the pulses [6]. Short-term BPV relates to changes in blood pressure that occur within 24 h and is characterized by regular circadian changes such as night-time blood pressure drop and morning blood pressure fluctuation [6]. A 24-hour ambulatory blood pressure measurement evaluates short-term BPV. In this technique, blood pressure is measured at intervals (usually 15–30 min) determined by the clinician day and night [1, 7]. Long-term BPV refers to changes in blood pressure daily, visit to visit, and season to season [6].

Anticholinergic drugs are agents that reduce or block the effects of acetylcholine on smooth muscle cells, glands, and parasympathetic nervous system receptors in the central nervous system. The undesirable effects caused by these agents are referred to as anticholinergic side effects [8]. Anticholinergic side effects can be examined in two groups, which are central and peripheral side effects. Peripheral side effects include decreased secretion, reduced gastrointestinal motility, constipation, urinary retention, vision problems, tachycardia, hypertension, hot intolerance, and hyperthermia. Anticholinergic central side effects occur due to decreased activity of acetylcholine in the brain, such as confusion, lack of focus, sedation, memory impairment, and decreased cognitive functions.

The anticholinergic burden is the cumulative effect of taking one or multiple drugs with anticholinergic properties [9]. The anticholinergic burden scale (ACB) is a four-point scale based on published data and expert opinions published by Boustani in 2008 and updated in 2012. Although the ACB scale was originally designed to assess the effects of anticholinergic drugs on cognitive functions, there are several studies in the current literature that evaluated the clinical impacts of ACB score on clinical outcomes other than cognitive functions, including risk of cardiovascular diseases, frailty, increased risk of ischemic stroke, the length of hospital stay, in-hospital mortality, unplanned intensive care unit admission, and unexpected readmissions [10–13]. The anticholinergic load of drugs is assessed by ACB scale with a score of 0 to 3, including no anticholinergic load (0 points), probable anticholinergic load (1 point), and definite anticholinergic load (2 or 3 points). The ACB scale includes 88 drugs with known anticholinergic activity [14–16].

In this study, we investigated the relationship between the ACB scale score caused by drugs used in individuals over 50 years of age and diagnosed with hypertension and short-term BPV.

Methods

Setting, participant characteristics and procedures

This prospective, single-center, and observational study was carried out with adult hypertensive patients aged 50 years and over receiving antihypertensive treatment. The participants were enrolled from internal medicine and cardiology outpatient settings of a university hospital between 01.07.2021 and 15.09.2022, and they were enrolled following an ambulatory blood pressure measurement that was conducted. Enrollees younger than 50 years old, without an existing diagnosis of hypertension, who have had medication added or removed from their treatment within the last 3 months, with end-stage cancer, end-stage heart failure, cirrhosis, a history of recent trauma or surgical intervention, with advanced dementia, and those who were hesitant to give written informed consent were excluded. Patients with missing data on key variables such as blood pressure measurements or medication records were not included in the study during the inclusion phase. Thus, no missing data imputation was required.

Explanation of aims and protocol of the study, taking history, recording of demographic characteristics including age and gender, alcohol use, smoking, recording of comorbid diseases including hypertension, diabetes mellitus, chronic ischemic heart disease, hypercholesterolemia, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and the calculation of ACB score of drugs used were carried out face-to-face in a private room under the guarantee of confidentiality based on participants statements. The sample size was calculated using the G* Power 3.1 software according to the following data, and the sample size was found to be 250. Ethical approval for this study was obtained from the Ethics Committee of the University of Health Sciences Gülhane Training and Research Hospital with the decision dated 23 June 2021 and numbered 2021/ E-50687469-799. A written informed consent was obtained from each participant at enrollment. All procedures followed the Turkish Medicine and Medical Devices Agency Good Clinical Practices Guidelines and the Declaration of Helsinki.

Calculation of anticholinergic burden

The ACB of the drugs used by the patients was calculated according to the scoring system of the Anticholinergic Burden Scale [17]. ACB is a scale based on a systematic literature review of drugs with known anticholinergic activity. It was published in the United States by Malaz Boustani in 2008 and was updated in 2012. The anticholinergic burdens of the drugs are evaluated with a score of 0 to 3, with no anticholinergic burden (0 points), possible anticholinergic burden (1 point), and

definite anticholinergic burden (2 or above). The ACB scale includes 88 drugs with known anticholinergic activity.

Administration of ambulatory blood pressure measurement and interpretation of short-term blood pressure variability

Ambulatory blood pressure was measured with the IEM Mobil-O-Graph device, and sleep and wake times were noted. Standard deviation (SD) of 24-hour consecutive blood pressure measurements, coefficient of variation of the SD (SD-CoV), and weighted mean SD (wSD) variables according to night and daytime were used for evaluating the results of ambulatory blood pressure measurements. Blood pressure decreases typically during sleep [4]. This circadian rhythm in blood pressure has led to a new classification. A decrease of 10% or more in the blood pressure measured at night compared to the daytime value is defined as dipper hypertension, and a decrease of less than 10% is defined as non-dipper hypertension. A higher rate of cardiovascular mortality and morbidity has been observed in patients with non-dipper hypertension [18, 19].

The ambulatory blood pressure meter calculated the SD of 24-hour consecutive blood pressure measurements. The SD-CoV was considered the value obtained by dividing the SD of the blood pressure measurement series by the arithmetic mean of the blood pressure measurements (SD/mean) series and multiplying the result by 100. The wSD according to night and day periods was obtained by adding 14 times the mean standard deviation of the day and 6 times the mean standard deviation of the night and dividing the sum by 20.

Table 1 Basic demographics and general characteristics of participants

	Total $n=238$
Age (years), median (IQR), [min-max]	70 (18) [50–98]
50–64 years, n (%)	83 (34.87)
≥65 years, n (%)	155 (65.13)
Female gender, n (%)	153 (64.29)
Comorbid Diseases	
Diabetes mellitus, n (%)	102 (42.86)
Chronic ischemic heart disease, n (%)	64 (26.89)
Congestive heart failure, n (%)	34 (14.29)
Chronic kidney disease*, n (%)	28 (11.76)
Atrial Fibrillation, n (%)	18 (7.56)
Chronic obstructive pulmonary disease, n (%)	12 (5.04)
Results of Ambulatory Blood Pressure Measurement	
SBP (mmHg), 24 h, mean (SD)	126.68 (16.47)
SBP (mmHg), Day interval, mean (SD)	127.58 (16.66)
SBP (mmHg), Night interval, mean (SD)	123.51 (17.42)
DBP (mmHg), 24 h, mean (SD)	74.59 (10.36)
DBP (mmHg), Day interval, mean (SD)	75.36 (10.61)
DBP (mmHg), Night İnterval, mean (SD)	72.18 (11.17)
MAP (mmHg), 24 h, mean (SD)	98.21 (12.31)
MAP (mmHg), Day interval, mean (SD)	99.06 (12.49)
MAP (mmHg), Night interval, mean (SD)	95.45 (13.16)
Dippers, n (%)	70 (29.41)

N: absolute number; IQR: interquartile range; Min: Minimum; Max: Maximum; SBP: systolic blood pressure; SD: Standard deviation; DBP: diastolic blood pressure; MAP: mean arterial pressure

Statistical analysis

The statistical analyses were performed with the 'Statistical Package for Social Sciences (SPSS) (Version 26.0, Chicago, Illinois). The Shapiro-Wilk test was used to test the normality of the data. The results were expressed as mean and SD for normally distributed continuous variables. Categorical data were presented as absolute numbers and percentages of the total. The differences between continuous variables were compared using the Student's T-Test for two groups and the One-Way ANOVA test for multiple groups. The differences between skewed variables were compared using the Mann-Whitney U test for two groups and the Kruskal Wallis test for multiple groups. The chi-square test was used to compare categorical variables. The relationship between age and ACB was evaluated by calculating the Pearson Correlation (r). The p-value was accepted as <0.05 for statistical significance.

Results

A total of 238 patients with a mean age of 70 (min:50, max:98, IQR:18) years were included in the study, and 35.71% ($n=85$) of the participants were male. The most common comorbid diseases other than hypertension noted among the participants were diabetes mellitus (42.86%, $n=102$), chronic ischemic heart disease (26.89%, $n=64$), and congestive heart failure (14.29%, $n=34$). The basic demographic and general characteristics of the participants were also given in Table 1.

Of the participants, 139 (58.40%) had no ACB score, 64 (26.89%) had an ACB score of 1, and 35 (14.71%) had an ACB score of 2 or above. While the use of drugs leading to higher ACB scores was significantly more frequent among atherosclerotic cardiovascular disease and congestive heart failure patients ($p<0.001$ for both), no such significance was observed among patients with diabetes mellitus ($p=0.069$), chronic kidney disease ($p=0.212$), and chronic obstructive pulmonary disease ($p=0.053$). In addition, the correlation test revealed that advancing age was strongly correlated with an increase in ACB ($r=0.308$, $p<0.001$).

The mean systolic blood pressure (SBP) of the participants was 126.68 (16.47) mmHg, the mean diastolic blood pressure (DBP) was 74.59 (10.36) mmHg, and the mean arterial pressure (MAP) was 98.21(12.31) mmHg (Table 1). The mean SBP, DBP, and MAP of the patients were similar among patients with no (ACB score = 0),

Table 2 The comparison of short-term blood pressure variability parameters of participants

	Total (*n* = 238)	ACB Score = 0 (*n* = 139)	ACB Score = 1 (*n* = 64)	ACB Score ≥ 2 (*n* = 35)	*P*
SBP-SD, mmHg, median (IQR)	13.50 (6.33)	13.10 (6.40)	14.05 (5.55)	14.40 (6.60)	0.489
SBP SD-CoV, median (IQR)	10.68 (3.80)	10.39 (4.30)	11.05 (3.12)	10.81 (2.99)	0.298
SBP wSD, median (IQR)	12.57 (5.67)	12.01 (5.74)	13.20 (5.06)	12.70 (5.62)	0.126
DBP-SD, mmHg, median (IQR)	9.65 (3.38)	9.70 (3.45)	9.60 (3.40)	9.80 (2.60)	0.904
DBP, SD-CoV, median (IQR)	13.10 (4.59)	12.62 (4.54)	13.13 (5.04)	13.92 (4.41)	0.518
DBP, wSD, median (IQR)	9.10 (3.03)	9.00 (2.88)	9.06 (3.32)	9.29 (2.72)	0.788
MAP-SD, mmHg, median (IQR)	10.00 (4.07)	9.90 (4.30)	10.05 (3.82)	10.30 (4.00)	0.946
MAP, SD-CoV, median (IQR)	10.23 (3.62)	10.22 (3.89)	10.23 (2.91)	10.68 (3.10)	0.992
MAP, wSD, median (IQR)	11.33 (4.62)	10.97 (4.92)	11.77 (4.28)	11.91 (4.37)	0.177
Dippers, n (%)	70 (29.41)	46 (19.33)	17 (7.14)	7 (2.94)	0.266

N: absolute number; ACB: anticholinergic burden; SBP: systolic blood pressure; SD: Standard deviation; IQR: Interquartile range; SD-CoV: Standard deviation-coefficient of variation; wSD: weighted standard deviation; DBP: diastolic blood pressure, MAP: mean arterial pressure; ACB: anticholinergic burden scale; $p < 0.05$ considered significant

Table 3 The comparison of short-term blood pressure variability parameters of participants

	Total (*n* = 238)	ACB Score = 0 (*n* = 139)	ACB Score ≥ 1 (*n* = 99)	*P*
SBP-SD, mmHg, median (IQR)	13.50 (6.33)	12.90 (6.40)	14.20 (5.70)	0.240
SBP SD-CoV, median (IQR)	10.68 (3.80)	10.39 (4.30)	10.96 (3.04)	0.120
SBP wSD, median (IQR)	12.57 (5.67)	12.01 (5.74)	14.08 (5.26)	0.051
DBP-SD, mmHg, median (IQR)	9.66 (3.38)	9.70 (3.45)	9.60 (3.10)	0.708
DBP, SD-CoV, median (IQR)	13.10 (4.59)	12.62 (4.54)	13.80 (4.79)	0.499
DBP, wSD, median (IQR)	9.10 (3.03)	9.00 (2.88)	9.20 (3.00)	0.562
MAP-SD, mmHg, median (IQR)	10.00 (4.07)	9.90 (4.30)	10.10 (3.90)	0.854
MAP, SD-CoV, median (IQR)	10.23 (3.62)	10.22 (3.89)	10.24 (2.84)	0.906
MAP, wSD, median (IQR)	11.33 (4.62)	10.97 (4.92)	11.78 (4.43)	0.065
Dippers, n (%)	70 (29.41)	46 (19.33)	24 (10.08)	0.140

N: absolute number; ACB: anticholinergic burden; SBP: systolic blood pressure; SD: Standard deviation; IQR: Interquartile range; SD-CoV: Standard deviation-coefficient of variation; wSD: weighted standard deviation; DBP: diastolic blood pressure, MAP: mean arterial pressure; ACB: anticholinergic burden scale; $p < 0.05$ considered significant

possible (ACB score = 1), or definite (ACB score ≥ 2) ACB ($p = 0.950$, $p = 0.820$, $p = 0.818$, respectively). The comparison of mean SBP, DBP, and MAP in participants 65 and over ($n = 155$) also revealed no difference between groups with ACB scores of 0, 1, and 2 ($p = 0.840$, $p = 0.880$, $p = 0.928$, respectively).

Among the patients, 29.41% (n:70) were evaluated as dipper and 70.59% (n:168) as non-dipper, and no relationship was found between the decrease in blood pressure at night and the ACB ($p = 0.266$).

The comparison of short-term BPV parameters, including SD, SD-CoV, and wSD of SBP, DBP, and MAP, revealed no significant relationship between short-term BPV and ACB ($p > 0.05$ for all). The compared values of each group and parameter were given in Table 2. The comparison results of short-term BPV parameters were also similar in participants aged 65 and over ($n = 155$) regarding patients with no (ACB score = 0), possible (ACB score = 1), or definite (ACB score ≥ 2) ACB ($p > 0.05$ for all parameters).

In addition, when the patients were divided into two groups: patients without ACB and those with ACB scores of 1 or above, and SD, SD-CoV, and wSD of SBP, DBP, and MAP were compared, the results similarly showed no significant relationship between any short-term BPV parameter and ACB score (Table 3) ($p > 0.05$ for all). Also, being either a dipper or a non-dipper hypertension patient was not associated with ACB ($p > 0.05$) (Tables 2 and 3).

Discussion

In this study, we assessed the relationship between ACB and short-term BPV in hypertensive patients over 50 years of age. Results revealed no statistically significant relationship between ACB and mean blood pressure, nocturnal blood pressure dips, or any parameters of short-term BPV.

In the literature search, we found no studies indicating a relationship between anticholinergic drug use and blood pressure variability or examining the relationship between anticholinergic drug load and short-term blood pressure variability. Recent studies on BPV have highlighted its adverse effects on cardiovascular outcomes, including increased mortality due to cerebrovascular

disease, coronary artery disease, end-stage renal disease, cardiovascular diseases, and overall mortality [20]. In addition, as people age, several underlying factors contribute to increased BPV, including hemodynamic instability, atherosclerosis, arterial stiffness, baroreflex dysfunction, endothelial impairment, and subclinical inflammation [21, 22]. These findings suggest that managing BPV and lowering absolute blood pressure levels may help achieve better cardiovascular protection in patients with hypertension [1].

A study by Reinold et al. using data from approximately 16 million patients in the German Pharmacoepidemiological Research Database found a significant relationship between anticholinergic burden, as measured by the ACB scale, and age [23]. Similarly, Valladales et al., in a study of 3,760 patients, reported that individuals aged 75 and older were more likely to be prescribed anticholinergic drugs, with one-third of them using at least one such drug at this age [24]. Our study also found a strong correlation between patients' age and ACB scores, which indicate the ACB of the drugs they used.

The use of drugs leading to higher ACB scores was significantly more frequent among the patients with congestive heart failure and atherosclerotic cardiovascular disease [25]. Similarly, in our study, the ACB score was significantly higher among the patients with congestive heart failure and atherosclerotic cardiovascular disease. This association may be linked to the ACB of certain medications used to manage atherosclerotic cardiovascular disease, including atenolol, metoprolol, digoxin, warfarin, captopril, nifedipine, and isosorbide mononitrate.

A study by L. Vetrano in Italy involving 3,761 elderly participants living in nursing homes examined the relationship between anticholinergic drug burden, hospitalization, and mortality. The study found a higher anticholinergic burden associated with increased hospitalization and all-cause mortality in this population [26]. Similarly, a study by Landi et al. investigating the use of anticholinergic drugs and their adverse effects in a frail elderly population reported a significantly higher frequency of heart failure in patients with a high anticholinergic drug burden [25].

Ayer et al. investigated the hemodynamic effects of parasympathetic blockade using a peripheral muscarinic antagonist, scopolamine methyl bromide, in rats. The study demonstrated that muscarinic receptor inhibition significantly increased blood pressure and BPV [27]. However, unlike the findings in rats, our study found no relationship between patients' short-term BPV and the anticholinergic burden of the drugs they used.

Our study has several limitations that should be considered when interpreting the results. First, the study was conducted at a single tertiary care center with a relatively small and young study population. This situation may limit the generalizability of the findings and may have resulted in lower cumulative exposure to anticholinergic medications and reduced BPV, potentially limiting the ability to detect statistically significant associations. Secondly, according to previous studies, autonomic dysfunction, neuropsychiatric, and sleep disturbances can arise in neurodegenerative diseases, resulting in BPV [28]. Considering we did not include patients with neurodegenerative diseases in our study cohort, we also did not assess such known contributors to BPV that may still influence the BPV in the absence of neurodegenerative diseases. Third, the ACB scale was originally designed to evaluate cognitive effects and does not account for muscarinic receptor subtype selectivity, drug interactions, treatment duration, dose dependency, or tolerance [29]. Although the ACB scale has been broadly applied in clinical studies, these pharmacologic limitations should be considered, and alternative tools such as the Anticholinergic Drug Scale or Drug Burden Index may offer more relevant perspectives for cardiovascular outcomes in further studies. Finally, due to its design, ACB scores were calculated without stratifying medications by drug class, which prevented the analysis of class-specific effects.

Conclusion

The elderly population is steadily increasing due to rising life expectancy and ACB also tend to rise with age. Increased BPV is independently associated with a higher risk of target organ damage, cardiovascular events, and mortality [20]. Therefore, BPV should be considered when evaluating hypertension patients' blood pressure.

Anticholinergic drugs are linked to various adverse outcomes in older adults, including increased falls, fractures due to falls, cognitive decline, the development of dementia, malnutrition, as well as higher rates of emergency department visits and hospitalizations [30, 31]. To minimize such risks associated with ACB, the use of drugs with anticholinergic side effects should be reduced, especially in elderly patients. Medications without anticholinergic properties should be prescribed, and the anticholinergic burden should be carefully considered when selecting medications.

This study did not find a statistically significant relationship between ACB and short-term BPV. Our literature review did not identify any studies that have investigated the relationship between anticholinergic drug use and short-term BPV. To the best of our knowledge, this is the first study to explore this potential connection in humans and may pave the way for more comprehensive research in this area.

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Nothing to declare.

Author contributions
Furkan KÖŞKER: Data collection, interpretation of data for the work, writing, critical reviewReşit Emre ALPARĞAN: Data collection, interpretation of data for the work, critical reviewMuhammed Ali COŞKUNER: Writing, interpretation of data for the work, Final approval of the version to be publishedGökhan KÖKER: Writing, interpretation of data for the work, critical reviewBilgin Bahadır BAŞGÖZ: Design, statistical analysis, interpretation of data for the work, writing, critical review, Final approval of the version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Clinical Research Ethics Committee of Health Sciences University Gülhane Training and Research Hospital approved the study protocol (approval date and number: 2021/ E-50687469-799), and a written informed consent was obtained from each participant before enrolled to the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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