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Blood pressure and neuropsychiatric symptoms in old age

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Chapter 3

Lower blood pressure and apathy coincide in older persons with lower functional ability. The DANTE Study Leiden



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Abstract

Background

We examined the association between blood pressure measures and symptoms of apathy and depression in older participants with various levels of functional ability.

Methods

Using baseline data from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) Study Leiden a cross-sectional study was performed. In four hundred thirty community-dwelling participants aged 75 years and above systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured during home visits. Symptoms of apathy and depression were assessed with the Apathy Scale and the Geriatric Depression Scale (GDS-15), respectively. Stratified linear regression was performed in participants with higher and lower functional ability according to the median of the Groningen Activity Restriction Scale.

Results

In participants with lower functional ability, each 10 mmHg lower SBP, DBP and MAP were associated with higher Apathy Scale scores (0.63, 0.92 and 0.94 points, respectively, all $P < 0.005$), but not with GDS-15 scores. In participants with higher functional ability blood pressure measures were not associated with Apathy Scale or GDS-15 scores.

Conclusion

In older participants with lower functional ability, lower blood pressure was associated with more symptoms of apathy, but not depression.

Introduction

Symptoms of apathy and depression are common in old age.¹ Apathy often occurs within the context of depression, but is also increasingly recognized as a distinct syndrome in which lack of motivation is a predominant feature.²

Observational studies have shown inconsistent results for the relationship between blood pressure (BP) with symptoms of apathy and depression in old age. Cross-sectional associations have been found between higher BP and symptoms of apathy^{3,4} and depression⁵ in community dwelling older persons. Contradictory, other studies have found lower BP to be cross-sectionally^{6,7} and longitudinally⁸ associated with symptoms of depression. Heterogeneity of population characteristics may underlie the variety of study outcomes.

Older persons of a similar chronological age appear to be highly heterogeneous in their biological age and, accordingly, in their functional ability. There is increasing evidence that the clinical implications for BP in old age depend on level of function ability. A prospective cohort study in the oldest old, showed that a lower, rather than a higher BP predicted cognitive decline.⁹ This relationship was most pronounced in those with pre-existing poor functional ability. Furthermore, in older persons with poor functional ability, a lower BP has been associated with increased risk of stroke¹⁰ and mortality.^{11,12} These findings suggest that a lower BP in older persons with lower functional ability may, possibly as a result of a dysfunctional vascular system, compromise cerebral perfusion with resulting adverse health outcomes.¹³ It is unclear whether the relationship between BP and symptoms of apathy and depression in older persons also depends on level of functional ability.

Community-dwelling persons aged 75 and older with mild cognitive dysfunction who were using antihypertensive medication and had a wide range of functional ability were recruited for the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden. This allowed us to examine cross-sectionally whether the association between BP and symptoms of apathy and depression differs between older persons with better and worse functional ability. It was hypothesized that, especially in older persons with worse functional ability, lower BP would be associated with more symptoms of apathy and depression.

Methods

Study design and participants

Data were obtained from the baseline assessment of the DANTE Study Leiden. This randomized controlled trial evaluates whether temporary discontinuation of antihypertensive medication in older participants with mild cognitive dysfunction improves cognitive and psychological functioning.

Individuals aged 75 years and older were recruited from primary care practices in the Netherlands between May 2011 and July 2013 (n=430). Inclusion criteria were a Mini-Mental State Examination (MMSE) score between 21 and 27, taking antihypertensive medication, and a current systolic BP (SBP) of 160 mmHg or less (140 mmHg in individuals with diabetes mellitus (DM), peripheral arterial disease, or a myocardial infarction (MI) or coronary reperfusion procedure >3 years before). Exclusion criteria were a history of stroke or transient ischemic attack (TIA), a recent (3 years) MI or coronary reperfusion procedure, current angina pectoris, cardiac arrhythmias, heart failure requiring antihypertensive medication, use of antihypertensive medication other than for hypertension, a clinical diagnosis of dementia, or limited life expectancy. The medical ethics committee of the Leiden University Medical Center approved the DANTE Study Leiden, and informed consent was obtained from all participants.¹⁴

Assessment of blood pressure

SBP and diastolic blood pressure (DBP) were measured twice in all participants in the sitting position using a digital sphygmomanometer on the right arm, with two minutes between measurements. For the analyses, the mean value of the two measurements was used. The mean arterial pressure (MAP) was calculated as $1/3*(SBP) + 2/3*(DBP)$ as a proxy for cerebral blood flow.¹⁵

Assessment of apathy and depression

Apathy was assessed using the Apathy Scale,¹⁶ a semi-structured interview scale consisting of 14 items (range 0-42 points), with higher scores indicating more-severe apathy. A score 14 or greater is indicative for the presence of clinically significant apathy.¹⁶ Depressive symptoms were assessed using the Geriatric Depression Scale (GDS)-15.¹⁷ This questionnaire consists of 15 items (range 0-15 points) with higher scores indicating more-severe depressive symptoms. A score of 5 or greater is indicative of clinically significant depressive symptoms.¹⁷

Assessment of functional ability

The Groningen Activity Restriction Scale (GARS)¹⁸ was used to examine functional ability. The GARS measures functional ability in activities of daily living (ADL, 11 items) and in instrumental activities of daily living (iADL, seven items), with higher scores indicating worse functional ability (range 18-72 points).

Demographic and clinical characteristics

Information on demographic and clinical characteristics was collected from participants in standardized interviews. Education was dichotomized at primary education (6 years of schooling), and use of alcohol was dichotomized at 14 U/wk. Medical history, including use of medication, was obtained for 426 participants from their general practitioner using structured questionnaires. Information was obtained on a set of chronic diseases to assess comorbidity: DM, chronic obstructive pulmonary disease (COPD), Parkinson's disease, malignancy, and osteoarthritis.^{19,20} History of cardiovascular disease (CVD) was also assessed. Because individuals with stroke or TIA were excluded from the DANTE Study Leiden, a history of CVD comprised a MI or coronary reperfusion procedure more than 3 years before or a history of peripheral arterial vascular disease. MMSE score at inclusion was used as a measure of global cognitive function and Stroop interference score (time to complete Stroop card 3—((time to complete Stroop card 1 + Stroop card 2)/2))²¹ as a measure of executive cognitive functioning. Current use of psychotropic medication comprised antipsychotic and antidepressant therapy, as well as the use of benzodiazepines.

Statistical analysis

Demographic and clinical characteristics in participants with better and worse functional ability are presented as numbers with percentages, means with standard deviations, or medians with interquartile ranges when appropriate. Characteristics were compared using Pearson chi-square tests for categorical variables, Student t-tests for continuous independent variables with normal distribution, and nonparametric Mann-Whitney tests for continuous independent variables with nonnormal distribution. The relationship between BP measures and symptoms of apathy and depression was tested in the entire sample using multiple linear regression models. Unstandardized betas (b) and 95% confidence intervals (CI) were calculated per 10-mmHg increase in BP measures. Age, sex, education, current smoking status, use of alcohol, history of CVD, number of chronic diseases, use of beta-blockers, current use of psychotropic medication, GARS score, and MMSE score were added as covariates in the adjusted model. Stroop interference score was added separately to the adjusted model to explore the influence of executive functioning on the findings. Interaction between the effect of functional ability (total GARS

score dichotomized on the median score of 22) and BP measures on symptoms of apathy and depression was tested by adding an interaction term in linear regression models. This analysis was performed to formally assess whether the association between BP measures and symptoms of apathy and depression was significantly different in persons with various levels of functional ability. Separate interaction analyses were performed for the IADL and ADL subscales (dichotomized on the median scores of 9 and 13, respectively) to further investigate whether an impairment of IADL, ADL or both determined this potential interaction effect of BP measures with level of functional ability. Stratified multiple linear regression analyses were performed to assess whether participants with worse and better functional ability (according to a score above or below the median GARS score of 22 points) have different associations between BP measures and Apathy Scale and GDS-15 scores. The association between BP measures and symptoms of apathy in participants without depressive symptoms, indicated by a score of less than 2 on a subscale of 12 items of the GDS-15 subscale, which indicates only symptoms of depressed mood and dissatisfaction with life and not symptoms of apathy, was tested in a sensitivity analysis.³ $P < .05$ was considered significant. All analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL).

Results

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics in strata of functional ability. Participants with a lower functional ability were older (83.1 ± 4.9 years versus 79.7 ± 3.5 years, $p < 0.001$) and less often male (65 (31.1%) versus 105 (47.7%), $p < 0.001$) in comparison to those with higher functional ability. Participants with worse functional ability were also less educated, more often used psychotropic medication, more often had at least one chronic disease, had lower executive functioning and had more symptoms of apathy and depression.

Association between blood pressure and symptoms of apathy and depression

In the entire population, lower BP measures were associated with more symptoms of apathy in the adjusted model (SBP: $\beta = -0.29$, $p = 0.006$, DBP: $\beta = -0.24$, $p = 0.23$, MAP: $\beta = -0.36$, $p = 0.03$), whereas only a lower SBP was associated with symptoms of depression ($\beta = -0.10$, $p = 0.04$).

TABLE 1. Characteristics of participants and by strata of functional ability (n=430)

Characteristics	Worse functional ability (GARS score >22, n=209)	Better functional ability (GARS score ≤22, n=220)	P-value ^a
Demographic			
Age, years, mean ±SD	83.1 ±4.9	79.7 ±3.5	<0.001
Male, n(%)	65 (31.1)	105 (47.7)	<0.001
≤ 6 years of education, n (%)	85 (40.7)	58 (26.4)	0.002
Clinical			
Current smoking, n (%)	20 (9.6)	19 (8.6)	0.74
Alcohol ≥14 U/week, n (%)	16 (7.7)	28 (12.7)	0.08
History of cardiovascular disease ^{b,c} , n (%)	28 (13.6)	20 (9.1)	0.15
Chronic disease ^{b,d} , n (%)	139 (67.5)	116 (53.0)	0.002
Use of antihypertensive medication ^b , n (%)			
Beta blocker	83 (40.1)	89 (40.6)	0.91
Diuretic	109 (52.7)	119 (54.3)	0.73
ACE inhibitor or ARB	140 (67.6)	141 (64.4)	0.48
Calcium channel blocker	53 (25.6)	50 (22.8)	0.50
Use of psychotropic medication ^b , n (%)	48 (23.2)	29 (13.2)	0.008
Benzodiazepines	26 (12.6)	21 (9.6)	0.33
Antidepressants	28 (13.5)	12 (5.5)	0.004
Antipsychotics	4 (1.9)	0 (0.0)	0.04
MMSE in points, median (IQR)	26.0 (25.0-27.0)	26.0 (25.0-27.0)	0.18
Stroop interference score, sec, median (IQR)	33.0 (23.3-53.6)	29.0 (20.0-44.0)	0.02
Systolic, mmHg, mean ±SD	146.9 ±22.0	148.5 ±21.0	0.43
Diastolic, mmHg, mean ±SD	80.0 ±11.3	82.0 ±10.5	0.05
Mean arterial pressure, mmHg, mean ±SD	102.8 ±13.9	104.2 ±12.5	0.13
Neuropsychiatric measures			
Apathy Scale, points, mean ±SD	12.6 ±5.0	10.2 ±4.1	<0.001
≥14 points, n (%)	82 (39.4)	42 (19.1)	<0.001
GDS-15, points, median (IQR)	2.0 (1.0-3.0)	1.0 (0.0-2.0)	<0.001
≥5 points, n (%)	32 (15.4)	13 (5.9)	0.001
Functional ability			
GARS points, median (IQR)	28.0 (25.0-34.0)	19.0 (18.0-20.0)	
ADL, points, median (IQR)	16.0 (14.0-19.0)	11.0 (11.0-12.0)	
iADL, points, median (IQR)	13.0 (10.5-15.0)	7.0 (7.0-8.0)	

One missing value on Groningen Activity Restriction Scale (GARS).

a Calculated for difference between groups with better and worse functional ability using Student t-test, Mann-Whitney test, and Pearson chi-square test where appropriate.

b Missing values: n = 4 in group with better functional ability and n = 3 in group with worse functional ability.

c Myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft ≥3 years before, peripheral arterial disease.

d Diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease, malignancy, osteoarthritis.

SD = standard deviation; IQR = interquartile range, MMSE=Mini-Mental State Examination, GDS=Geriatric Depression Scale, ADL=Activity of Daily Living, iADL= instrumental Activity of Daily Living, ACE= angiotensin-converting enzyme inhibitor, ARB= angiotensin receptor blocker

In the crude and adjusted model, tests of the effect of the interaction between SBP, DBP and MAP and the level of functional ability (total GARS score) regarding Apathy scale scores were significant (all p-values for interaction terms ≤ 0.005). Additional interaction analyses between BP measures with iADL or ADL subscales of the GARS regarding Apathy scale scores, showed that significant interaction was present for iADL, but not for ADL (data not shown). In contrast, no interaction was present between the BP measures and the level of functional ability regarding GDS-15 scores.

Stratified analyses shown in Table 2 show that, in participants with worse functional ability, lower BP was associated with higher Apathy Scale scores. In the adjusted model, for participants with worse functional ability, each 10-mmHg lower SBP, DBP, and MAP was associated with a 0.63 ($P < .001$), 0.92 ($P = .003$), and 0.94 ($P < .001$) point higher score on the Apathy Scale, respectively. Additional adjustment for executive function gave largely similar estimates. In participants with better functional ability, BP measures were not associated with Apathy Scale scores. Furthermore, BP measures were not associated with GDS-15 scores in either stratum of functional ability. Figure 1 shows the association between BP measures and the Apathy Scale and GDS-15 scores according to level of functional ability. Figure 1 shows the opposite directions of the effect of BP on symptoms of apathy in participants with better and worse functional ability.

A sensitivity analysis of the association between BP and symptoms of apathy in 302 participants without depressive symptoms showed similar directions of effect and largely similar effect sizes for both strata of functional ability (data not shown).

TABLE 2. Mean Apathy Scale scores in groups of blood pressure measures, stratified by Level of Functional Ability

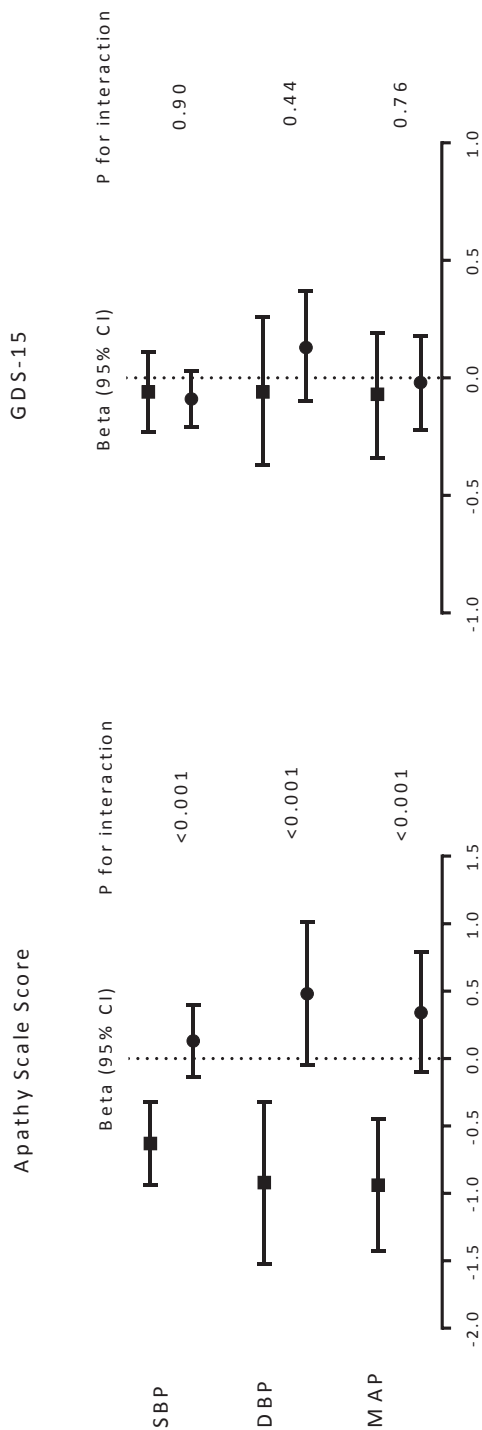
	Worse functional ability (GARS score >22, n=209)			Better functional ability (GARS score ≤22, n=220)			p-value	p-value
	Groups of blood pressure measures	Beta (95% CI)	p-value	Groups of blood pressure measures	Beta (95% CI)	p-value		
SBP, mmHg	<140, n=79	140-160, n=74	>160, n=56	<140, n=83	140-160, n=75	>160, n=62		
Crude model	14.1 (0.6)	11.6 (0.6)	11.9 (0.7)	9.9 (0.5)	9.9 (0.5)	10.9 (0.5)	0.001	0.13
Adjusted model*	14.3 (0.6)	11.6 (0.6)	11.6 (0.7)	9.9 (0.5)	10.0 (0.5)	10.6 (0.5)	<0.001	0.35
DBP, mmHg	<80, n=104	80-90, n=69	>90, n=36	<80, n=88	80-90, n=85	>90, n=47		
Crude model	13.4 (0.5)	11.7 (0.6)	12.0 (0.8)	9.7 (0.4)	10.6 (0.4)	10.3 (0.6)	0.01	0.15
Adjusted model*	13.6 (0.5)	11.8 (0.6)	11.3 (0.8)	9.6 (0.4)	10.7 (0.5)	10.3 (0.6)	0.003	0.08
MAP, mmHg	<97, n=70	97-108, n=71	>108, n=68	<99, n=74	99-108, n=72	>108, n=74		
Crude model	14.0 (0.6)	12.2 (0.6)	11.7 (0.6)	9.4 (0.5)	10.6 (0.5)	10.5 (0.5)	0.002	0.10
Adjusted model*	14.4 (0.6)	12.1 (0.6)	11.2 (0.6)	9.4 (0.5)	10.6 (0.5)	10.4 (0.5)	<0.001	0.13

P-values were calculated using systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) as continuous variables. Betas represent change in Apathy Scale score per 10-mmHg increase in blood pressure. Range of instruments: GARS 18-72, Apathy Scale 0-42.

*Adjusted for sex, age, education, current smoking, use of alcohol, history of cardiovascular disease, number of chronic diseases, use of psychotropic medication, use of beta blockers, and Mini Mental State Examination score.

CI = confidence interval; GARS = Groningen Activity Restriction Scale.





■ n=209 persons with a lower functional ability according to GARS >22
 ● n=220 persons with a higher functional ability according to GARS ≤22.

FIGURE 1. Change in Apathy Scale or Geriatric Depression Scale (GDS)-15 score per 10 mmHg increase in blood pressure measures, stratified on level of functional ability

Analyses were adjusted for gender, age, education, current smoking, use of alcohol, history of cardiovascular disease, number of chronic diseases, use of psychotropic medication, use of beta blockers and MMSE. SBP= systolic blood pressure; DBP= diastolic blood pressure; MAP= mean arterial pressure; GARS= Groningen Activity Restriction of life Scale, range GARS score: 18-72, median GARS score=22.

Discussion

In older persons with worse functional ability, lower SBP, DBP and MAP were associated with more symptoms of apathy, but not with symptoms of depression.

Contradictory to our findings, two cross-sectional studies suggested a relationship between a higher BP and apathy,^{3,4} although these studies included community-dwelling older persons, who were about 10 years younger than participants in the current study. Moreover, these studies did not consider functional ability as an effect modifier. Previous studies found a cross-sectional^{6,7} and longitudinal association⁸ for lower BP and symptoms of depression. We found no such association in either stratum of functional ability. This discrepancy may be due to limited power, taking into consideration the low prevalence of symptoms of depression in our study population. However, it cannot be excluded that lower BP was truly not associated with symptoms of depression, but only with symptoms of apathy. It has been suggested before that apathy and depression have different risk factors and etiologies.¹⁹

The current study found that interaction between level of functional ability and various BP measures regarding Apathy Scale score was present for iADL, but not for ADL. This may be because the iADLs subscale is more sensitive than the ADL subscale for detecting subtle changes in functional ability in our population with an overall high level of functional ability.¹⁸

It is not possible to make causal inferences from this cross-sectional observational study, but explanations for the findings can be speculated on. First, the relationship between lower BP and symptoms of apathy in participants with worse functional ability may be due to better treatment of higher BP in participants with more comorbid diseases (who are at risk for symptoms of apathy), although BP measures were not significantly lower in participants with worse functional ability than in those with better functional ability. Second, lower BP may not be causally related to symptoms of apathy in older persons with worse functional ability but may instead share a cause, such as cardiac dysfunction. Cardiac dysfunction can precede lower BP,²² worse functional ability²³ and symptoms of apathy.²⁴ However, persons with clinical heart failure were excluded from participation. Moreover, an equal proportion of participants with better and worse functional ability had a history of cardiovascular disease. Additionally, adjustment for this factor did not change the observed association. Third, incipient dementia may precede a lower BP,²⁵ functional impairment²⁶ and symptoms of apathy.²⁷ Although persons with dementia were excluded, participants with worse functional ability had a lower level of executive cognitive functioning than those with higher functional ability. Nevertheless, similar results were found after additional adjustment for executive function. Finally, an alternative explanation may be that lower BP in older persons with worse functional ability might compromise cerebral perfusion as a result of a failing vascular system and thereby increase the risk of symptoms of apathy.

This study has several strengths. Validated measures were used to assess symptoms of apathy and depression. That symptoms of depression did not confound the relationship between lower BP and symptoms of apathy was clearly demonstrated, because a sensitivity analysis in participants without depressive symptoms showed similar results. Nevertheless, there are limitations to be considered when interpreting the results. First, no causal inference can be made because of the study's cross-sectional observational design. Second, because no neuroimaging data were available, it was not possible to ascertain that worse functional ability coincided with lower cerebral perfusion. Third, participants were using antihypertensive treatment and had no history of stroke, TIA, or recent MI, which limits the extrapolation of the findings to the general population of the older old. Finally, only the GARS was used to estimate functional ability. Although there is no single criterion or definition for functional ability, GARS score may not fully reflect functional ability in daily life. Given the limitations, the results should be interpreted with caution. The findings contribute to increasing observational evidence that lower BP is associated with adverse health outcomes in older persons with worse functional ability.¹³ Therefore, future studies should determine whether older persons with poor functional ability could benefit from less-stringent BP targets to prevent symptoms of apathy and other adverse health outcomes. If so, worse functional ability may become an important criterion for treatment decisions regarding antihypertensive medication.

In conclusion, functional ability moderates the association between BP and symptoms of apathy. Older persons with poor functional ability and low BP had more symptoms of apathy than those with high BP.

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