Orthostatic Changes in Blood Pressure and Cognitive Status in the Elderly
The Progetto Veneto Anziani Study

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Abstract—We studied a cohort of 1408 older subjects to explore whether postural changes in blood pressure (BP; defined as orthostatic hypo- or hypertension) can predict the onset of cognitive deterioration. Orthostatic hypotension was defined as a drop of 20 mm Hg in systolic or 10 mm Hg in diastolic BP and orthostatic hypertension as a rise of 20 mm Hg in systolic BP. Orthostatic BP values were grouped into quintiles for secondary analyses. Two cognitive assessments were considered: (1) cognitive impairment, that is, Mini-Mental State Examination scores ≤24/30, and (2) cognitive decline (CD), that is, a 3-point decrease in Mini-Mental State Examination score from the baseline to the follow-up. At the baseline, the prevalence of orthostatic hypotension and hypertension was 18.3% and 10.9%, respectively. At the follow-up (4.4±1.2 years), 286 participants were found cognitively impaired and 138 had a CD. Using logistic regression analysis adjusted for potential baseline confounders, participants with orthostatic hypertension were at significantly higher risk of CD (odds ratio =1.50; 95% confidence intervals =1.26–1.78). Neither orthostatic hypotension nor orthostatic hypertension raised the risk of developing a cognitive impairment. Using quintiles of orthostatic BP values, we found that both decreases and increases in systolic and diastolic BP raised the risk of CD, but not of cognitive impairment. In conclusion, we found that orthostatic hypertension predicts the onset of CD, but not of cognitive impairment in the elderly, whereas orthostatic hypotension predicts neither of these conditions. Further studies are needed to confirm our findings.
(Hypertension. 2016;68:427-435. DOI: 10.1161/HYPERTENSIONAHA.116.07334.) • Online Data Supplement

Key Words: blood pressure ■ cognition ■ cognitive impairment ■ elderly ■ orthostatic hypertension ■ orthostatic hypotension

Cognitive impairment (CI) and cognitive decline (CD) are common among older people and can be considered as conditions lying along a continuum from cognitively normal aging to dementia.[1,2]

Several factors are important for the onset of CI and CD, including female sex and the apolipoprotein Eε4 (apoEε4) genotype.[3,4] Changes in blood pressure (BP) are associated with both CI and CD in older people.[5,6] Hypertension might be implicated in the pathogenesis of poor cognition,[7] and recent studies suggest that hypotension could be a risk factor for CI and CD too.[8] This association has not been thoroughly investigated for orthostatic changes in BP, however.

The type of orthostatic BP dysregulation most often studied is orthostatic hypotension, identifiable in ≈20% to 30% of individuals over 65 years of age.[9,10] Although both orthostatic hypotension and poor cognitive status are common in the elderly, few studies have explored the potential longitudinal influence of orthostatic hypotension on cognitive function, and they have generated inconsistent findings. Some authors found orthostatic hypotension unassociated with CI or CD in geriatric patients,[11,12] whereas others reported a significant link.[13,14] Meanwhile, the possible relationship between orthostatic hypertension and cognitive status has never been considered, though this condition is a risk factor for several other negative outcomes in the elderly, such as cardiovascular diseases, essential hypertension, and mortality.[11,15]

We hypothesized that both orthostatic hypotension and orthostatic hypertension might carry a risk of being associated with cognitive deterioration. The aim of the present study was thus to explore whether postural changes in BP could predict

DOI: 10.1161/HYPERTENSIONAHA.116.07334

the onset of CI and CD in a cohort of community-dwelling older subjects.

Methods

Data Source and Subjects

This work was based on data obtained for the Progetto Veneto Anziani (Pro.V.A.) study, an observational cohort study of community-dwelling subjects aged ≥65 years residing in Camposampiero and Rovigo (2 towns in northern Italy), who were enrolled without any specific exclusion criteria.[16] Baseline visits were conducted between October 1995 and November 1997. To avoid any sampling bias, the initial sample was randomly divided into 3 (Camposampiero) and 4 (Rovigo) mutually exclusive subsets that were balanced for age and sex distribution. A random sample was selected from the first subset, and the remaining subsets were set aside. As part of the sampling strategy, age and sex were stratified to maintain a male-to-female ratio of 2:3, to oversample the oldest subjects and thereby obtain reliable estimates of conditions with low prevalence rates, and to recruit a sizable proportion of disabled individuals. The follow-up was scheduled 4 years after the baseline assessment.

The ethical committees of Padua University and the Veneto Region's Local Health Units (Unita Locale Socio Sanitaria) no 15 and no 18 approved the study protocol, and participants gave their written informed consent to the study.

Clinical Data

Participants were examined at city hospitals by trained physicians and nurses. A face-to-face interview was used to collect information on their social and demographic characteristics, smoking habits, and the number and type of drugs they used. Regular physical activity was defined as ≥4 h/week in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing, or physical exercising). Smoking habits were categorized as current versus previous smokers (if someone had given up smoking at least a year earlier) versus nonsmokers. Educational level was categorized as ≤5 versus >5 years (because primary school lasts 5 years in Italy). Monthly income was categorized as ≤500 € versus >500 €. Body weight and height were measured by trained physicians, and the body mass index (kg/m²) was calculated.

Any diseases were assessed by board-certified physicians, who considered all the clinical details collected for each participant in the study (clinical history, symptoms self-reported by means of standardized questionnaires, medical and hospital records, blood tests), and conducted a physical examination, also recording any cases of diabetes mellitus, general hypertension, cardiovascular disease, and cancer. Diabetes mellitus was defined as the fulfilment of at least one of the following criteria: fasting plasma glucose ≥7.0 nmol/L, hemoglobin A1c ≥6.5%, use of glucose-lowering drugs, and history of 2-hour postload glucose ≥11.1 nmol/L.[17] Hypertension was defined as a systolic BP ≥140 mm Hg, a diastolic BP ≥90 mm Hg, or ongoing use of antihypertensive medication.[18] As cardiovascular diseases, we considered positivity for any of the following: congestive heart failure, angina requiring a stent or angioplasty or hospitalization, myocardial infarction, stroke, atrial fibrillation, or peripheral artery disease.

Multidimensional Assessment

A multidimensional assessment was conducted by physicians expert in geriatric medicine. Functional status was assessed using the scores for activities of daily living and instrumental activities of daily living. Depressed mood was assessed with the 30-item Geriatric Depression Scale, a depression rating scale validated for use in the elderly, where a score of ≥10/30 is suggestive of depression.[19]

Definition of Orthostatic Hypertension and Hypotension

All BP measurements were taken by a trained nurse in the morning. Clinostatic BP was measured in the right arm 3×, with 30-second intervals between measurements, using a mercury sphygmomanometer (Erkameter 300), in participants who had been supine for at least 5 minutes, taking the mean value as the clinostatic readings.

Orthostatic BP was then measured after 1 and 3 minutes of orthostatism. In agreement with the guidelines of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology, orthostatic hypotension was defined as a drop of at least 20 mm Hg in systolic BP or at least 10 mm Hg in diastolic BP in one of the 2 measurements.[20] Because no formal consensus exists on how orthostatic hypertension should be defined, we adopted the most often used definition for this condition, that is, an increase in systolic BP in excess of 20 mm Hg calculated as the mean of the systolic BP measurements obtained during orthostatism minus the clinostatic BP before standing.

We also ran a secondary analysis on quintiles of changes between orthostatic and clinostatic systolic and diastolic BP, based on a method proposed by Fan et al.[15] For this analysis, we took the mean orthostatic BP at 1 and 3 minutes and applied the following cut offs to divide the sample into quintiles: −11, −3, +2, and +9 mm Hg for systolic BP and −1, +2, +6, and +10 mm Hg for diastolic BP.

Cognitive Assessment

Cognitive function was assessed at the baseline and follow-up by administering the 30-item Mini-Mental State Examination (MMSE), the repeated use of which is capable of measuring changes in cognitive status.[21] The crude MMSE scores obtained in our sample were adjusted for age and formal education using coefficients recommended for the Italian population. Adjusted scores ≤24 were indicative of CI; and a drop of ≥3 points in the MMSE score from baseline to follow-up was defined as a CD.[22] In a sensitivity analysis, we explored whether any differences came into light in a composite outcome taking CI or CD and the loss of one activities of daily living or instrumental activities of daily living or institutionalization during follow-up into account.

Statistical Analyses

Participants' characteristics were summarized using means (±standard deviations) for continuous variables and counts and percentages for categorical variables. The normality of the distribution of the continuous variables was assessed with the Shapiro–Wilk test. Means and proportions were compared between participants grouped by orthostatic changes in BP using age- and sex-adjusted P values calculated for continuous variables with a generalized linear model, applying a Bonferroni's correction, and with a logistic regression for categorical variables.

Known factors associated with orthostatic BP changes or cognitive status were considered for inclusion in the analysis. A univariate analysis was performed, taking a $P \leq 0.10$ as a criterion for inclusion in the fully adjusted model. Collinearity was quantified using the variance inflation factor, adopting a cut off of 2. In the fully adjusted analysis, a stepwise selection was used to obtain the set of variables most effective in predicting cognitive status at follow-up. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare the onset of CI or CD across orthostatic BP changes, taking participants with normal postural changes for reference. Using a similar approach, a Cox's regression analysis was run, considering all-cause mortality as outcome.

A similar analysis was also conducted using the quintiles of the orthostatic changes in systolic and diastolic BP, taking the quintile that included the mean (=Q3 in both cases) for reference. Generalized linear models were used to examine the association between baseline orthostatic changes in BP and changes in MMSE scores during the follow-up, using the same covariates as in the fully adjusted model for the OR analyses. The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time. Because this test returned a value <0.05, we used a logistic regression analysis to assess the association between orthostatic changes in BP and cognitive status at the follow-up.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc, Chicago, IL). All statistical tests were 2-tailed, and statistical significance was assumed for a P value <0.05.

Results

Selection of Participants

Among the 3099 subjects initially enrolled, no baseline orthostatic BP data were available for 142 individuals, 1212 had a diagnosis of CI already at the baseline, and another 10 had a diagnosis of Parkinson's disease. Another 241 participants died before attending the follow-up and 86 failed to attend, leaving a final sample of 1408 subjects eligible for the present study (Figure 1).

Baseline Data

The sample thus consisted of 1408 participants cognitively normal at the baseline (572 male and 836 female), with a mean age of 71.4±5.2 years (range: 65–96) and a mean baseline MMSE score of 27.2±1.8 points. Most of the participants were between 65 and 69 years old (as shown in Figure S1 in the online-only Data Supplement). The prevalence of orthostatic hypotension and hypertension was 18.3% and 10.9%, respectively.

After grouping the sample by orthostatic changes in BP (hypotension versus normal postural changes in BP versus hypertension), those with normal postural changes were found to be significantly younger than those with orthostatic hypotension, and they were more frequently male than in either of the other 2 groups (Table 1). After adjusting for age and sex, those with normal postural changes in BP were significantly better educated and more likely to be smokers than participants in the other 2 groups. They also had lower

Figure 1. Flow-chart. MMSE indicates Mini-Mental State Examination; and Pro.V.A., *Progetto Veneto Anziani*.

Geriatric Depression Scale scores and less cardiovascular disease or general hypertension than the group with orthostatic hypotension and higher instrumental activities of daily living scores, more cardiovascular disease, and more cancers than the group with orthostatic hypertension (Table 1). No differences in MMSE were apparent across groups (Table 1). As for drug use, participants in the orthostatic hypotension group were more frequent users of antihypertensive medication (at both baseline and follow-up) than those in the other 2 groups, whereas those with orthostatic hypertension were more likely to have started taking antihypertensive medication during the follow-up. The group with orthostatic hypertension also reported less use of anticoagulants and benzodiazepines than the other 2 groups, whereas the group with orthostatic hypotension made more use of antidepressants (Table 1). Finally, the group with orthostatic hypotension had higher mean clinostatic systolic and diastolic BP values than the other 2 groups (Table 1).

Follow-Up Data

By the time of the follow-up (after a mean 4.4 years), 241 participants had died. As shown in Figure S2, those with orthostatic hypotension had a significantly higher risk of dying than those with normal postural changes (hazard ratio =1.20, 95% confidence intervals [CI] 1.06–1.66; P=0.03). After adjusting for potential confounders, this association was no longer significant, however (hazard ratio =1.00, 95% CI 0.72–1.34; P=0.45). Orthostatic hypertension was not associated with any increased mortality risk. During the follow-up, 286 participants (20.3%) were diagnosed with CI and 138 (9.8%) with CD (Table 2).

In the fully adjusted logistic regression analysis, taking participants with normal postural changes in BP for reference, neither orthostatic hypotension nor orthostatic hypertension raised the risk of CI at follow-up, but the group with orthostatic hypertension carried a significantly higher risk of CD (OR=1.50, 95% CI 1.26–1.78; P<0.0001; Table 2). In a sensitivity analysis, we explored the association between orthostatic changes in BP and CI/CD associated with disability or institutionalization at follow-up. Among 286 participants with CI, 270 had concomitant impairments in activities of daily living or instrumental activities of daily living or had been institutionalized and the same applied to 133 of the 138 participants with CD. Here again, the association was only significant between orthostatic hypertension and CD (OR=1.49, 95% CI 1.24–1.79; P<0.0001), not for CI. After removing 443 subjects who were depressed at the baseline, the association between orthostatic hypertension and CD remained, though it was attenuated (OR=1.21, 95% CI 1.08–1.78; P=0.002).

After adjusting for potential confounders, the changes in MMSE scores from baseline to follow-up showed that the group with orthostatic hypertension experienced a significantly greater drop in MMSE score (Δ=−2.1±5.6 points) than the group with orthostatic hypotension (Δ=−1.6±4.3 points, P=0.01), but not versus the group with normal postural changes in BP (Δ=−1.8±4.7 points; P=0.04; Figure 2).

We also checked whether differences between the mean systolic and diastolic orthostatic BP (measured at 1 and 3 minutes) and the clinostatic BP might influence our results. In the fully adjusted logistic regression analysis, taking participants
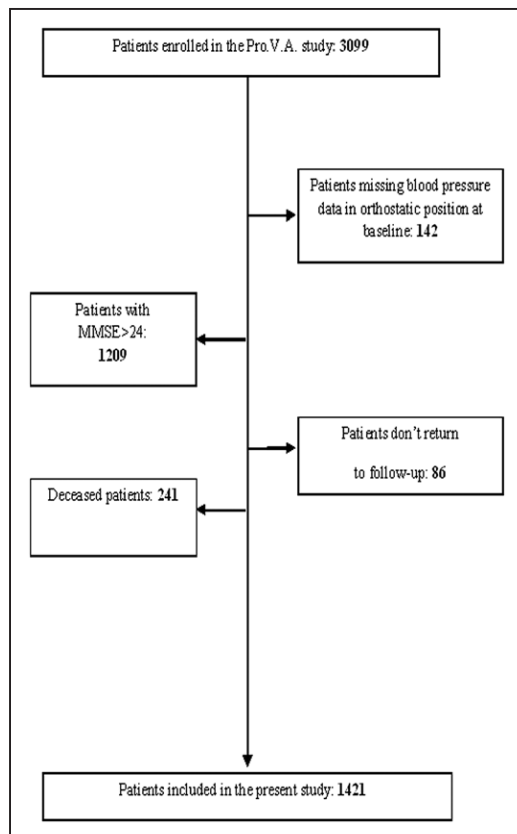
Table 1.   Baseline Characteristics by Orthostatic Changes in Blood Pressure: The Pro.V.A. Study (Weighted Data)

Variables	Normal Postural Changes (n=997)	Orthostatic Hypotension (n=258)	Orthostatic Hypertension (n=153)	Normal Postural Changes vs Orthostatic Hypotension P Value	Normal Postural Changes vs Orthostatic Hypertension P Value	Orthostatic Hypotension vs Orthostatic Hypertension P Value	Overall Comparisons P Value*
Demographic and social characteristics							
Age, y	71.0 (5.0)	72.3 (5.7)	72.2 (5.6)	<0.0001	0.002	1.000	<0.0001†
Female sex, %	55.8	66.8	61.3	<0.0001	<0.0001	<0.0001	<0.0001†
BMI, kg/m²	27.9 (4.4)	27.8 (4.5)	27.9 (4.0)	1.000	1.000	1.000	0.515
Education level (>5 y)	23.4	17.7	16.5	<0.0001	<0.0001	0.155	<0.0001
Monthly income >500 €, %	44.2	42.7	44.2	0.090	0.154	0.960	0.320
Physical activity ≥4 h/wk, %	31.8	31.2	29.3	0.433	0.027	0.031	0.106
Previous smokers, %	34.6	27.1	30.2	0.090	0.832	0.018	<0.0001
Current smokers, %	12.1	9.0	8.7	0.037	0.005	0.327	<0.0001
Multidimensional assessment							
ADL score	5.6 (0.8)	5.6 (0.7)	5.6 (0.7)	1.000	1.000	1.000	0.766
IADL score	7.0 (1.1)	6.8 (1.2)	6.7 (1.4)	0.078	0.036	1.000	<0.0001
GDS score	8.9 (4.7)	9.7 (5.1)	8.7 (4.9)	0.027	1.000	0.057	<0.0001
MMSE score	27.3 (1.8)	27.1 (1.7)	27.0 (1.8)	0.141	0.396	1.000	0.604
Medical conditions							
Diabetes mellitus, %	13.5	13.8	13.2	0.966	0.488	0.855	0.856
Hypertension, %	71.1	79.1	70.5	<0.0001	0.443	<0.0001	<0.0001
Cardiovascular diseases, %	15.2	18.5	12.8	<0.0001	0.003	<0.0001	<0.0001
Cancer, %	6.4	6.7	5.0	0.800	0.027	0.036	0.073
Drug use							
Low-dose aspirin, %	12.6	12.2	12.7	0.551	0.689	0.946	0.843
Anticoagulants, %	1.8	1.3	0.7	0.022	0.001	0.091	0.001
Benzodiazepines, %	18.2	17.4	15.4	0.015	0.001	0.206	0.017
Any Antihypertensives (baseline), %	45.7	53.8	43.9	<0.0001	0.004	<0.0001	<0.0001
Used already at baseline, %	51.7	60.7	59.2	<0.0001	<0.0001	0.586	<0.0001
Adopted during follow-up, %	6.0	6.9	15.3	0.001	<0.0001	<0.0001	<0.0001
Antidepressants, %	4.1	6.0	3.3	<0.0001	0.082	<0.0001	<0.0001
Total drugs	2.3 (2.0)	2.6 (2.0)	2.3 (2.0)	0.576	1.000	0.267	0.288
Blood pressure measurements							
Mean clinostatic systolic BP, mm Hg	151.6 (20.3)	159.5 (22.1)	152.1 (21.5)	<0.0001	<0.0001	<0.0001	<0.0001
Mean clinostatic diastolic BP, mm Hg	84.7 (10.8)	87.6 (10.8)	82.1 (10.9)	<0.0001	0.030	<0.0001	<0.0001
1-min orthostatic systolic BP, mm Hg	149.9 (22.0)	137.1 (25.7)	166.5 (25.5)	<0.0001	<0.0001	<0.0001	<0.0001
1-min orthostatic diastolic BP, mm Hg	89.5 (12.4)	85.2 (13.9)	92.4 (13.3)	<0.0001	<0.0001	<0.0001	<0.0001
3-min orthostatic systolic BP, mm Hg	153.8 (21.2)	147.2 (22.7)	176.3 (22.6)	<0.0001	<0.0001	<0.0001	<0.0001

(Continued)

Table 1.   Continued

Variables	Normal Postural Changes (n=997)	Orthostatic Hypotension (n=258)	Orthostatic Hypertension (n=153)	Normal Postural Changes vs Orthostatic Hypotension *P* Value	Normal Postural Changes vs Orthostatic Hypertension *P* Value	Orthostatic Hypotension vs Orthostatic Hypertension *P* Value	Overall Comparisons *P* Value*
3-min orthostatic diastolic BP, mm Hg	89.9 (12.3)	87.8 (12.3)	93.6 (13.1)	<0.0001	<0.0001	<0.0001	<0.0001
Mean clinostatic heart rate, bpm	70.4 (13.0)	69.6 (11.3)	69.9 (10.6)	0.009	0.350	1.000	<0.0001
1-min orthostatic heart rate, bpm	77.2 (13.3)	78.7 (14.0)	78.3 (14.2)	<0.0001	0.004	1.000	<0.0001
3-min orthostatic heart rate, bpm	75.1 (13.1)	76.2 (14.9)	74.9 (12.5)	<0.0001	1.000	0.005	<0.0001

Numbers are mean values (and standard deviations) or percentages (%), as appropriate. ADL indicates activities of daily living scale; BMI, body mass index; BP, blood pressure; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living scale; MMSE, Mini-Mental State Examination; and Pro.V.A., *Progetto Veneto Anziani.*

*Unless otherwise specified, *P* values are adjusted for age and sex using a generalized linear model (with Bonferroni's correction) or logistic regression, as appropriate.

†Not adjusted for age or sex.

in the third quintile for reference, the other quintiles of systolic BP changes carried no greater risk of CI (Figure 3A), but a significantly higher risk of CD (Figure 3B). With the exception of those in Q5, participants in the other quintiles also had a significantly greater drop in their MMSE scores than those in Q3 (Figure 3C). No significant association emerged between changes in diastolic BP and CI (Figure 4A), whereas both lower and higher quintiles of diastolic BP changes carried a significantly higher risk of CD than the reference quintile, Q3 (Figure 4B). Only participants in Q5 experienced a significantly greater reduction in their MMSE scores during the follow-up than those in Q3, however (Figure 4C).

Discussion

In this prospective study, we found that orthostatic changes in BP significantly predicted CD, but not CI, and that orthostatic hypertension was more strongly associated with CD than did orthostatic hypotension.

Epidemiology of Orthostatic Hypotension and Hypertension

The prevalence of orthostatic hypotension and hypertension found in our sample (18.3% and 10.9%, respectively) is consistent with previous reports on these conditions.[15,23,24]

Our participants with orthostatic hypotension had more conditions likely to affect cognition (eg, depression, cardiovascular disease, general hypertension), whereas those with orthostatic hypertension had a better profile in this sense. These factors had little effect on baseline cognitive status, however, because no significant differences emerged in the MMSE scores across groups (orthostatic hypotension versus normal postural changes in BP versus orthostatic hypertension). As for the influence of medication, participants with orthostatic hypotension were more often users of antihypertensive drugs than those in the other 2 groups, suggesting an important role for these drugs in predicting poor cognitive status. Other studies concerned with the use of antihypertensive medication and cognition have produced contrasting results: some authors

have claimed that BP-lowering treatment leads to changes in physiological mechanisms of cerebral autoregulation and thereby exacerbates CD,[25] whereas others suggest that antihypertensive medication might prevent brain damage.[26]

Orthostatic Hypertension Raises the Risk of Cognitive Decline

At the follow-up, our group with orthostatic hypertension was found to carry a higher risk of CD. The estimated risk was ≈50% and was unaffected by potential confounders. To the best of our knowledge, this is the first report to show a significant association between orthostatic hypertension and cognitive status. In general, there is a dearth of information relating to the orthostatic hypertension among the elderly and hardly any knowledge as to its clinical significance and implications, but it may be a new risk factor for cerebral hypoxic damage and incident CD in elderly.[27] In other studies, it has been demonstrated that the prevalence of silent cerebrovascular disease is significantly higher in subjects with orthostatic hypertension.[24,28] Thus, we hypothesized that systemic hemodynamic atherosclerotic syndrome could have a part to play. This condition is typical of older people with orthostatic hypertension, and it is characterized by a synergistic risk of excessive hemodynamic stress (exaggerated variability in BP and blood flow) and vascular disease because of anatomic changes that may lead to damage and hypoxia in several vital organs, including the brain.[24] However, other research is needed about the impact of systemic hemodynamic atherosclerotic syndrome on cognitive performance.

Orthostatic Hypotension Does Not Predict Cognitive Degeneration

Orthostatic hypotension was unassociated with CD or CI in our sample, a finding in partial contrast with the literature. In a recent report on 1480 Swedish community-dwelling older people, orthostatic hypotension raised the risk of mild CI by 84% at 5-year follow-up. The authors only adjusted their analyses for age and education, however, making it difficult

Table 2. Association Between Changes in Orthostatic Blood Pressure and Cognitive Status: the Pro.V.A. Study (Weighted Data)

Exposure Parameter	No of Events*	No of People*	Unadjusted Odds Ratio (95% CI)	P Value	Fully Adjusted Model (OR with 95% CI)	P Value
Cognitive impairment						
Normal postural change	191	997	1 [reference]		1 [reference]	
Orthostatic hypotension	61	258	1.32 (1.19–1.46)	<0.0001	1.01 (0.90–1.15)	0.82
Orthostatic hypertension	34	153	1.26 (1.11–1.44)	<0.0001	0.99 (0.85–1.15)	0.86
Cognitive decline						
Normal postural change	98	997	1 [reference]		1 [reference]	
Orthostatic hypotension	20	258	0.80 (0.69–0.93)	<0.0001	0.78 (0.69–1.05)	0.08
Orthostatic hypertension	20	153	1.36 (1.16–1.59)	<0.0001	1.50 (1.26–1.78)	<0.0001

Unless otherwise specified, data are presented as odds ratios (OR) and 95% confidence interval (CI). The fully adjusted model was adjusted for age (continuous); sex; body mass index (continuous); activities of daily living score; baseline Mini-Mental State Examination score; positivity for cardiovascular disease; cancer; educational level (≤5 vs >5 y); monthly income (≥500 € vs <500 €); smoking status (categorized as never, former, and current); physical activity level (≥4 vs <4 h/wk); use of anticoagulants, benzodiazepines, antihypertensive agents (already at baseline or adopted during follow-up), antidepressants (all yes vs no); and number of drugs. Pro.V.A. indicates *Progetto Veneto Anziani*.

*Unweighted data.

to compare their findings with ours.[13] Our results are consistent with those of other longitudinal studies that found no differences in MMSE score between subjects with and without orthostatic hypotension at 2- and 4-year follow-up.[12,29] Our data suggest that the association found in other reports between orthostatic hypotension and CD may be the consequence of other factors or conditions that share the same pathogenesis as orthostatic hypotension.[30] It may also be that different results stem from different groups being compared (we only compared our participants with orthostatic hypotension with participants who had normal postural changes in BP, whereas other studies compared them with participants who had orthostatic hypertension too). A final consideration concerns the finding that orthostatic hypotension was associated with a higher mortality rate than orthostatic hypertension, though this association disappeared after correcting for potential confounders.[31] Nevertheless, recent studies have found a relationship between orthostatic hypotension, with a severe decline in diastolic BP and all-cause mortality in older people.[32] Therefore, the observed higher mortality in orthostatic hypotension might be a consequence of dysfunctional regulatory autonomic function or myocardial ischemia.[23,32]

Changes in Systolic and Diastolic Orthostatic Blood Pressure Raise the Risk of Cognitive Decline

In a secondary analysis, we explored whether using quintiles of orthostatic BP values generated different results from those based on a priori definitions. Taken together, our results showed that both increases and decreases in orthostatic BP were associated with CD at follow-up, suggesting a U-shaped relationship. The literature on the influence of orthostatic changes in BP and cognitive status is limited. In the one study available to date,[33] on a large cohort, a greater drop in systolic and diastolic BP on standing coincided with a worse global cognitive performance. It has been demonstrated that higher systolic and diastolic BP levels are associated with a greater prevalence of severe periventricular and subcortical

white matter lesions.[34] Other pathogenic mechanisms may be involved too, such as blood–brain barrier disruptions or cerebral edema.[35]

Our present findings should be taken with some caution, however, because orthostatic changes in BP were unable to predict CI in our sample. There could be several reasons for this, including the duration of the follow-up (which may have been too short to detect important changes in MMSE vis-à-vis the baseline) or changes in participants' use of medication or other conditions during the follow-up that we did not consider in our analyses. Further studies are needed to test whether orthostatic changes in BP are able to predict CI and dementia.
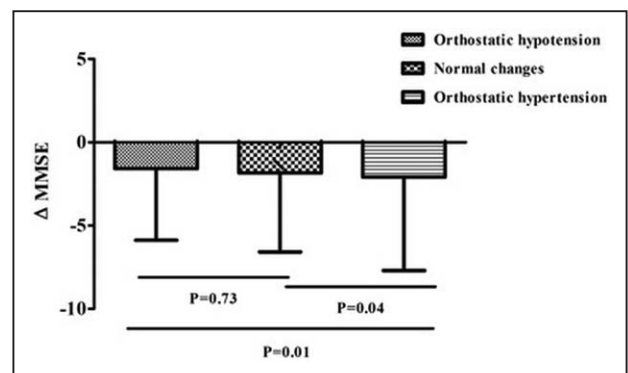

Figure 2. Changes in Mini-Mental State Examination (MMSE) scores from baseline to follow-up by baseline orthostatic changes in blood pressure: the *Progetto Veneto Anziani* (Pro.V.A.) study (weighted data). A generalized linear model (GLM) with Bonferroni's correction was used, including the following covariates: age (continuous); sex; body mass index (continuous); activities of daily living score; baseline Mini-Mental State Examination score; positivity for cardiovascular diseases, cancer (all yes vs no); educational level (≤5 vs >5 years); monthly income (≥500 € vs <500 €); smoking status (categorized as never, former, and current); physical activity level (≥4 vs <4 h/wk); use of anticoagulants, benzodiazepines, antihypertensive agents (already at baseline or adopted during follow-up), antidepressants (all yes vs no); and number of drugs.
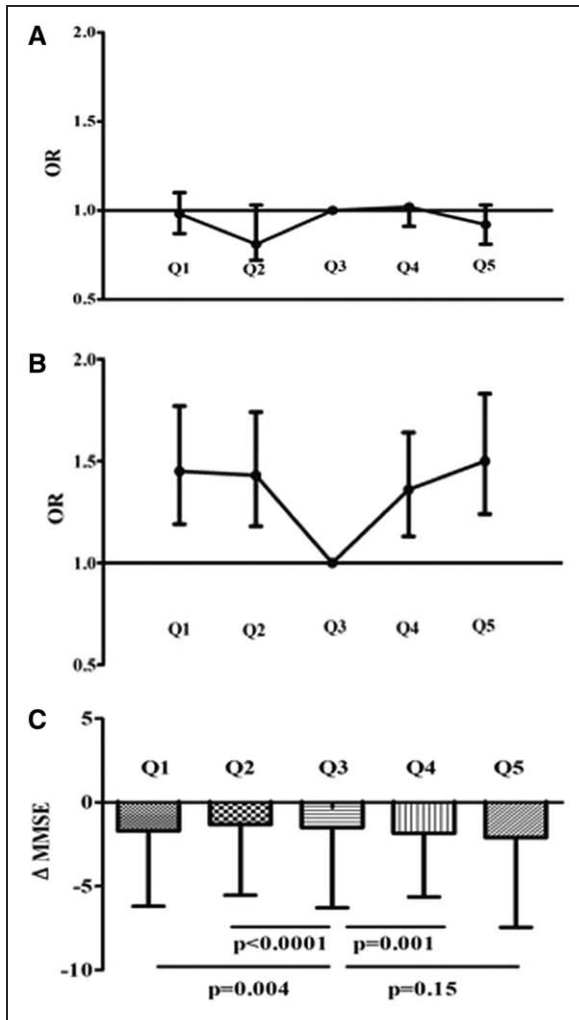
Figure 3. Association between orthostatic changes in systolic blood pressure (in quintiles) and cognitive status: the *Progetto Veneto Anziani* (Pro.V.A.) study (weighted data). Cognitive impairment (**A**); cognitive decline (**B**); changes in Mini-Mental State Examination scores (MMSE; **C**) from baseline to follow-up. A generalized linear model (GLM) with Bonferroni's correction was used, including the following covariates: age (continuous); sex; body mass index (continuous); activities of daily living score; baseline Mini-Mental State Examination score; positivity for cardiovascular diseases, cancer (all yes vs no); educational level (≤5 vs >5 years); monthly income (≥500 € vs <500 €); smoking status (categorized as never, former, and current); physical activity level (≥4 vs <4 h/wk); use of anticoagulants, benzodiazepines, antihypertensive agents (already at baseline or adopted during follow-up), antidepressants (all yes vs no); and number of drugs. OR indicates odds ratio.

Figure 4. Association between orthostatic changes in diastolic blood pressure (in quintiles) and cognitive status: the *Progetto Veneto Anziani* (Pro.V.A.) study (weighted data). Cognitive impairment (**A**); cognitive decline (**B**); changes in Mini-Mental State Examination scores (MMSE; **C**) from baseline to follow-up. A generalized linear model (GLM) with Bonferroni's correction was used, including the following covariates: age (continuous); sex; body mass index (as continuous); activities of daily living score; baseline Mini-Mental State Examination score; positivity for cardiovascular diseases, cancer (all yes vs no); educational level (≤5 vs >5 years); monthly income (≥500 € vs <500 €); smoking status (categorized as never, former, and current); physical activity level (≥4 vs <4 h/wk); use of anticoagulants, benzodiazepines, antihypertensive agents (already at baseline or adopted during follow-up), antidepressants (all yes vs no); and number of drugs. OR indicates odds ratio.

Limitations

The present study has some limitations. The first may concern the adoption of MMSE scores to assess global cognitive function because this tool inadequately explores verbal or visual memory.[36] Because MMSE is scarcely applicable to highly educated people or patients with vascular cognitive disorders, future studies should use more appropriate tools (such as the MoCa) to better elucidate whether changes in BP during orthostatism can affect specific memory domains. Studies like the recently undertaken SPRINT MIND (Systolic Blood Pressure Intervention Trial: Memory and Cognition in
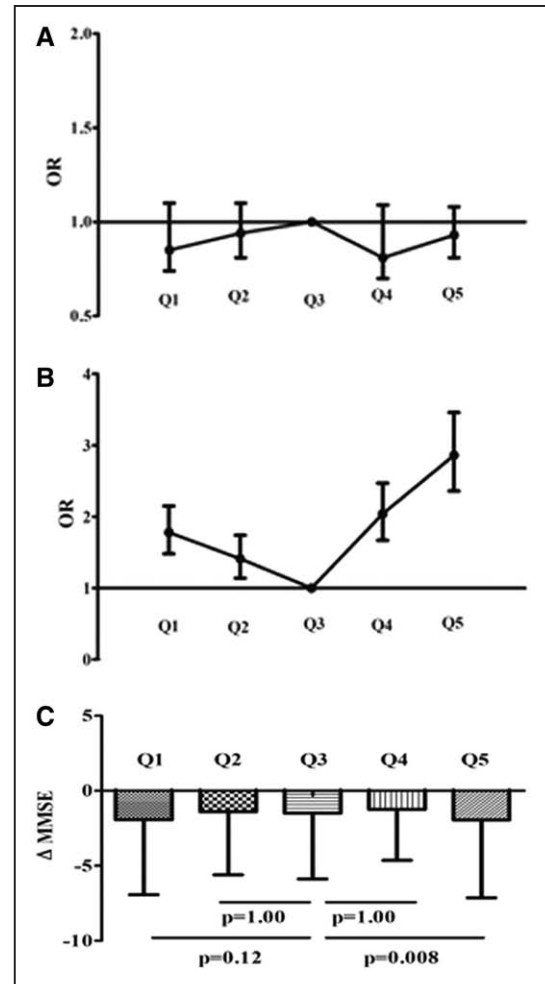
Decreased Hypertension) will be important in clarifying the association between BP and cognition.

Another limitation of our study lies in that we used no additional diagnostic techniques (such as brain imaging or cerebral spinal fluid analysis) to shed light on the type of any CI identified. We also used standing BP measurements, which are only a first-line test for identifying orthostatic changes in BP; other tests (eg, tilting the head up) would be more accurate in diagnosing orthostatic changes in BP. Another shortcoming lies in that we only conducted one session of clinostatic and orthostatic BP measurements and only over a period of 3 minutes, which may not be optimal for defining orthostatic hypo- or hypertension in an elderly cohort. A final limitation

lies in that a sizable proportion of our participants died during the follow-up and that not having taken them into account in our analyses may have given rise to a considerable confounding bias.

Perspectives

In conclusion, orthostatic hypertension predicted the onset of CD, but not of CI, in our sample of older subjects, whereas orthostatic hypotension predicted neither of these conditions. A U-shaped relationship emerged on using quintiles of orthostatic BP measurements, however, suggesting that further studies are needed to confirm our findings.

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Novelty and Significance

What Is New?

- The possible relationship between orthostatic hypertension and cognitive status has never been analyzed, despite the condition being a risk factor for several other negative outcomes in the elderly, such as cardiovascular diseases, essential hypertension, and mortality.
- To the best of our knowledge, this is the first report showing a significant association between orthostatic hypertension and cognitive status.

What Is Relevant?

- Our data suggest that orthostatic hypertension in the elderly is a risk factor for cerebral hypoxic damage and incident cognitive decline, probably because of a disturbed cerebral autoregulation.
- Older people with orthostatic hypertension should therefore undergo screening for the early identification of poor cognitive status.

Summary

In older people, orthostatic hypertension predicted the onset of cognitive decline, but no cognitive impairment, whereas orthostatic hypotension predicted neither of these conditions. Further studies are needed to confirm our findings.

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Orthostatic Changes in Blood Pressure and Cognitive Status in the Elderly: The Progetto Veneto Anziani Study

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ORTHOSTATIC CHANGES IN BLOOD PRESSURE AND COGNITIVE STATUS IN THE ELDERLY: THE PRO.V.A STUDY

Running title: Orthostatic blood pressure and cognitive status

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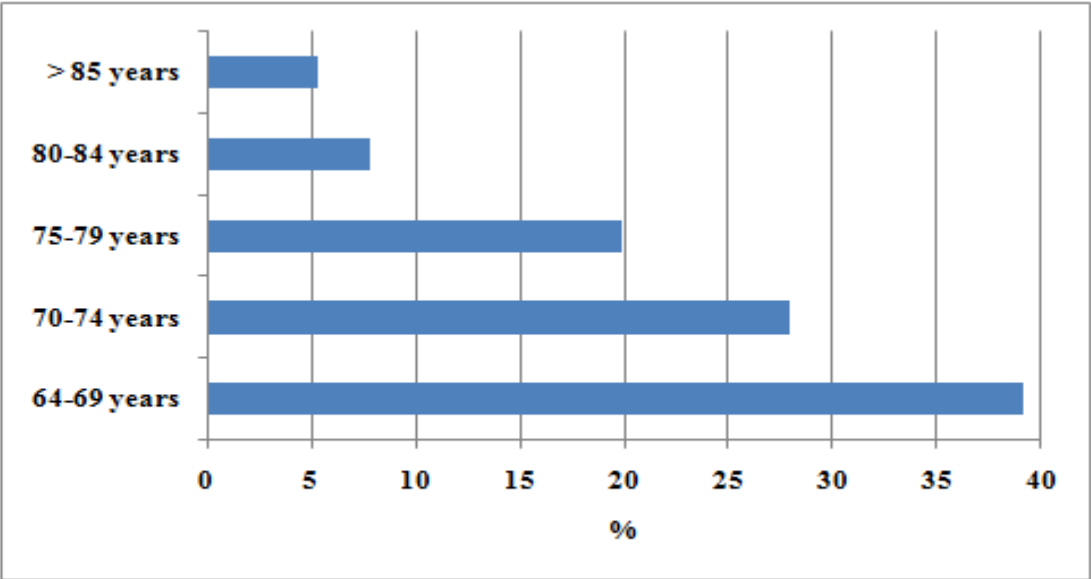
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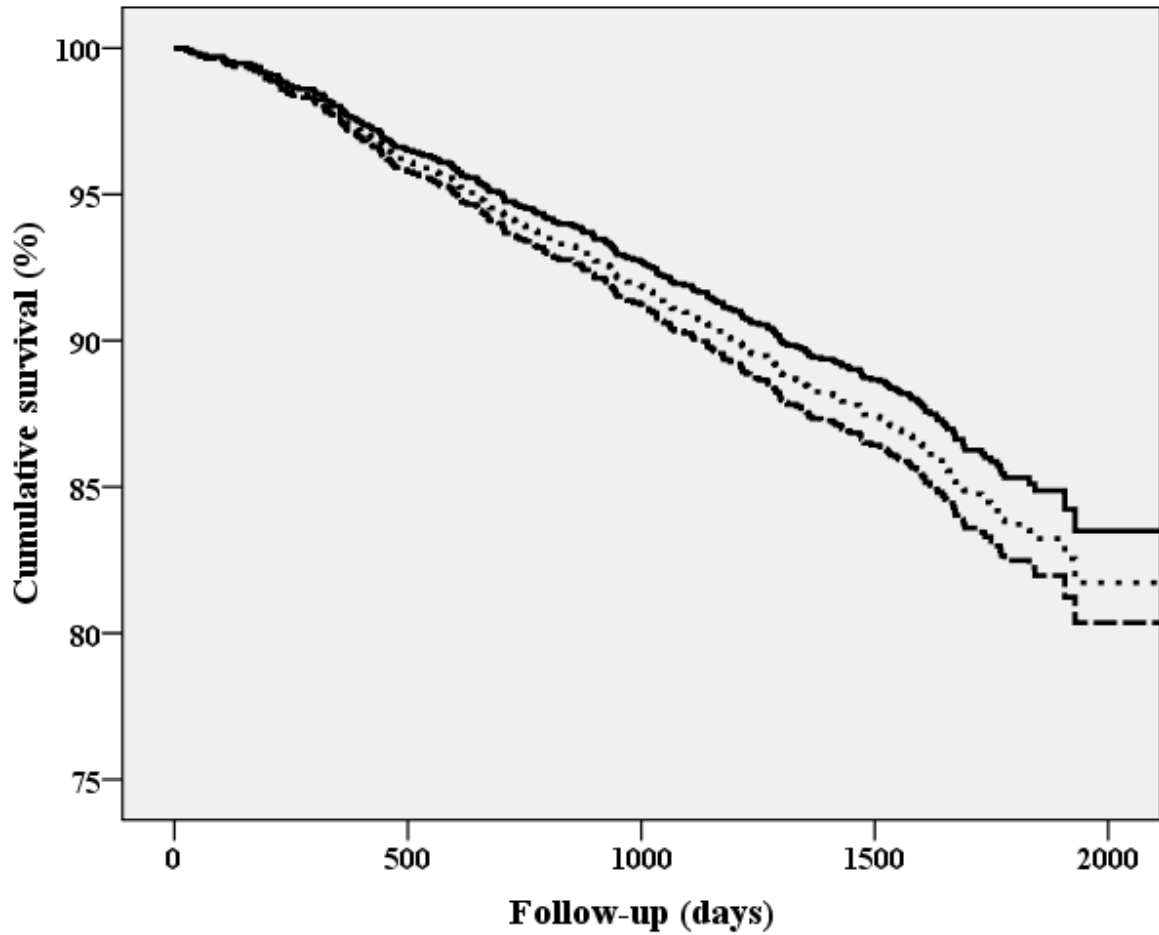Via Giustiniani, 2 - 35128 Padova, Italy

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Figure S1. Age distribution in the sample included: the PRO.V.A. study.

Notes: the bars indicate the prevalence (as percentage) for each 5 years interval.

Figure S2. Survival curves, by changes in orthostatic blood pressure at baseline.

Notes: the continuous line indicates those with normal changes in blood pressure during orthostatism; the pointed line indicates those with orthostatic hypertension; the dashed line the participants with orthostatic hypotension.