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Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension

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Abstract

Cognitive impairment and elevated arterial stiffness have been described in patients with arterial hypertension, but their association has not been well studied. We evaluated the correlation of arterial stiffness and different cognitive domains in patients with hypertension compared with those with normotension. We evaluated 211 patients (69 with normotension and 142 with hypertension). Patients were age matched and distributed according to their blood pressure: normotension, hypertension stage 1, and hypertension stage 2. Cognitive function was assessed using the Mini-Mental State Examination, Montreal Cognitive Assessment, and a battery of neuropsychological evaluations that assessed six main cognitive domains. Pulse wave velocity was measured using a Complior device, and carotid properties were assessed by radiofrequency ultrasound. Central arterial pressure and augmentation index were obtained using applanation tonometry. The hypertension stage 2 group had higher arterial stiffness and worse performance either by Mini-Mental State Examination (26.8±2.1 vs 27.3±2.1 vs 28.0±2.0, P=.003) or the Montreal Cognitive Assessment test (23.4±3.5 vs 24.9±2.9 vs 25.6±3.0, P<.001). On multivariable regression analysis, augmentation index, intima-media thickness, and pulse wave velocity were the variables mainly associated with lower cognitive performance at different cognitive domains. Cognitive impairment in different domains was associated with higher arterial stiffness.

1 | INTRODUCTION

Cognitive impairment and dementia have become serious human, social, and economic burdens.[1,2] The World Health Organization and the G8 Dementia Summit[2,3] emphasized prevention as a key element to counteract the dementia epidemic. There is increasing evidence that cardiovascular disease and its risk factors contribute to the development of cognitive impairment.[4] Thus, the relationship of high blood pressure (BP) with cognitive function and dementia has, in recent years, received much attention from epidemiological researchers, resulting in inconsistent observations.[5] Recent evidence has indicated that hypertension and its severity is associated with cognitive impairment.[6,7]

Arterial stiffness is increasingly recognized as an important prognostic indicator of cardiovascular events and a potential therapeutic target in patients with hypertension. It is closely linked to, but by no means synonymous with, elevated BP, and its physiopathology is still not fully understood. Aortic stiffness and arterial pulse wave

reflections are key determinants of elevated central systolic pressure and are associated with adverse cardiovascular outcomes, independent of BP.[8]

Many studies have demonstrated an association of vascular factors and cerebrovascular disease with dementia and cognitive decline.[9,10] Recently, some studies have reported an association between increased arterial stiffness, measured by pulse wave velocity (PWV), and poor cognitive function, and have suggested that arterial stiffness may be a determinant of cognitive decline and dementia.[11,12]

In the Rotterdam Study, however, the authors did not find an association between arterial stiffness, expressed as mean and standard deviation PWV, and cognitive decline or the risk of dementia. Although they found associations between arterial stiffness and several domains of cognitive function in cross-sectional analyses, these associations were small and, after adjustment for mean arterial pressure, heart rate, and cardiovascular risk factors, only the association between increased PWV and poor performance on the Stroop Test remained significant.[13]

Thus, up to now, identifying cerebrovascular risk factors that predict cognitive decline and dementia has been challenging but is regarded as extremely important among researchers and clinicians all over the world. If identified, such risk factors might be used to target individuals in whom modifiable risk factors should be mitigated.

Considering that previous findings regarding arterial stiffness and cognition in hypertension have been controversial, further investigations are warranted. Therefore, the aim of the present study was to investigate the association between arterial stiffness and cognition (assessed with general mental status measures and domain-specific tests) in a sample of patients with normotension and those with hypertension. The hypothesis of the present study was that patients with hypertension with higher arterial stiffness would have worse cognitive performance.

2 | METHODS

In a cross-sectional study, 211 patients (69 with normotension and 142 with hypertension) were evaluated. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and a neuropsychological evaluation battery.

Patients with the following conditions were excluded: age younger than 18 years, overt cerebrovascular disease (previous stroke or transient ischemic attack), diabetes mellitus, smoking, arrhythmias, heart failure with left ventricular dysfunction, known neurodegenerative or psychiatric disease, and illiteracy. Educational level was based on the number of school years completed. The local ethics committee approved the protocol, and all participants gave written informed consent.

2.1 | BP measurement

Brachial systolic and diastolic BP was assessed with an Omron automatic device, HEM-705 CP model, in the right upper arm, with the patient seated, after resting for 5 minutes following the recommendations of the VI Brazilian hypertension guidelines.[14] A mean of three measurements with a 1-minute interval was calculated and used to determine systolic and diastolic BP in each patient.

Patients with hypertension were divided into two groups according to BP levels or medication use (hypertension stage 1: BP 140–159/90–99 mm Hg or BP under control with one or two antihypertensive drugs; hypertension stage 2: BP ≥160/100 mm Hg or BP under control with ≥3 drugs). Three groups were comparatively analyzed: normotension, hypertension stage 1, and hypertension stage 2. Controlled hypertension was defined as BP levels <140/90 mm Hg with the use of antihypertensive drugs. The normotension group participants were recruited among patients without cardiovascular disease followed yearly at the Heart Institute as part of a protocol for cardiovascular assessment.[15]

2.2 | Cognitive function evaluation

2.2.1 | Mini-Mental State Examination

The MMSE is a commonly used 30-point scale to assess cognitive function in the areas of orientation, registration, attention and calculation, recall, language, and praxis. MMSE administration was performed according to existing standards.[16] On the MMSE, a score of ≤23 is usually an accepted cutoff, indicating the presence of cognitive impairment. However, many authors have recommended the adjustment to different cutoffs, considering the level of education and not a limited cutoff score.[17]

2.2.2 | Montreal Cognitive Assessment

The MoCA was designed as a rapid screening instrument to identify mild cognitive impairment.[18] It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points, and a score of 26 or above is considered normal. A previous validation study in Brazil suggested 25 points as the ideal cutoff for mild cognitive impairment identification.[19] To counterbalance the effect of lower education, one point was added to the final score of those individuals with <12 years of education.[18]

2.2.3 | Neuropsychological Evaluation

Procedures and descriptions of the neuropsychological tests used have been published elsewhere.[20-27] The neuropsychological test battery included the Boston Naming Test (BNT),[20] Rey Auditory Verbal Learning Test (RAVLT5: sum of 5 recall trials of 15 words; RAVLT6: immediate recall after interference; RAVLT7; delayed recall after 30 minutes),[24] the Rey-Osterrieth Complex Figure Test copy and delayed recall (REY-C and REY-30),[25] Semantic Verbal Fluency animal category (VF),[21] Phonological Verbal Fluency (FAS),[23] Forward and Backward Digit Span Test (FDST and BDST),[28] Trail Making Test part

A and B (TMT-A and TMT-B),[22] Clock Drawing Test (CDT),[26] and Digit Symbols Substitution Test (DSST).[27]

We computed scores for global cognition (mean *z* score of the BNT, RAVLT5, RAVLT6, RAVLT7, REY-C, REY-30, VF, FAS, FDST, BDST, TMT-A, TMT-B, CDT, and DSST), language (BNT), episodic memory (mean *z* score of the RAVLT5, RAVLT6, RAVLT7 and REY-30), executive functioning (mean *z* score of the VF, FAS, BDST, and TMT-B), visuospatial abilities (mean *z* score of the REY-C and CDT), attention (mean *z* score of the FDST and TMT-A), and processing speed (DSST).

z scores were calculated using persons without hypertension (control) as the reference group. Participants were considered to have cognitive impairment if they had scores below −1.5 standard deviation on one or more cognitive domains.

2.3 | Arterial stiffness

Carotid-femoral PWV was analyzed with a noninvasive automatic device, Complior (Colson), and carotid measurements (intima-media thickness [IMT] and carotid diameter) were made with a high-definition echo-tracking device (Wall Track System, Medical Systems Arnhem) by an experienced observer blinded to the clinical condition of each participant. All measurements were taken between 1 PM and 4 PM, with the patient in a recumbent position while awake. The PWV measurement technique has been previously described previously.[29,30] Briefly, common carotid artery and femoral artery pressure waveforms were recorded noninvasively by using a TY-306 Fukuda pressure-sensitive transducer (Fukuda). The pressure waveforms were digitized at the sample acquisition frequency of 500 Hz. The two pressure waveforms were then stored in a memory buffer. A preprocessing system automatically analyzed the gain in each waveform and adjusted it for the equality of the two signals. When the operator observed a pulse waveform of sufficient quality on the computer screen, digitization was suspended and calculation of the time delay between the two pressure upstrokes was initiated. Measurements were repeated over 10 different cardiac cycles, and the mean was used for the final analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites (D), whereas pulse transit time (t) was automatically determined by the Complior device; PWV was automatically calculated as PWV D/t, and we used 80% of this distance as pulse wave traveled distance (common carotid artery-common femoral artery × 0.8).[31] The validation of this automatic method and its reproducibility has been previously described.[30] Carotid diameter and IMT were evaluated with a high-resolution echo-tracking system (Wall Track System, Medical Systems Arnhem) coupled with conventional two-dimensional vascular echography (Sigma 44 Kontrom Instruments) equipped with a 7.5- MHz probe. Measurements were performed on the left common carotid arteries 1 cm below the bifurcation at the site of the distal wall. IMT was measured at the thickest point, not including plaques, on the near and far walls with a specially designed computer program. A high rate of IMT reproduction has been previously demonstrated.[32] Plaque was defined as a localized thickening >1.2 mm that did not uniformly involve the whole artery. Aortic distension as the systo-diastolic variation was automatically calculated. The SphygmoCor system (AtCor Medical) was used for central BP estimation, augmentation index (AIx), and augmentation index normalized for a heart rate of 75 beats per minute (AIx75), was used as a measure of arterial pressure wave reflection. The SphygmoCor measurement technique has been described elsewhere.[33] In brief, applanation tonometry was performed on the left radial artery with the patient seated. This was performed by lightly applying a micromanometer-tipped probe to the left radial artery over the extended wrist, compressing the vessel wall sufficiently so that transmural forces within the vessel wall were perpendicular to the arterial surface. All recorded readings were seen to meet the manufacturer's quality-control standards integrated into the software package.

Once the majority of the patients with hypertension had PWV values below the cutoff point (10 m/s) and the analysis by this cutoff was not feasible because of the small sample of patients above this recommended value (6 out of 142), we dichotomized this variable taking into account the mean PWV (7.9 m/s) in the hypertension group. This analysis was to evaluate whether higher PWV, even though below the reference cutoff, was associated with lower cognitive performance.

2.4 | Statistical analysis

Data were analyzed with SPSS for Windows 21.0 (IBM Corporation). Data distribution was determined using the Kolmogorov-Smirnov test. Continuous variables are presented as mean and standard deviation or as median and range if they were not normally distributed and they were analyzed by the independent samples *t* test and Mann-Whitney test when suitable. Categorical data are presented as percentages. The analysis of variance test with Bonferroni post hoc comparisons was used for continuous variables. The Kruskal-Wallis test was used for categorical variables. The Pearson coefficient was used for bivariate correlations. In multivariable regression analyses, all variables with $P<.1$ in unadjusted analysis were selected for multivariable linear stepwise analysis. To account for group differences in education, this variable was included as a covariate in the models. Statistical significance was set at 5%.

3 | RESULTS

Baseline characteristics of the study sample are described in Table 1. The three groups were similar regarding age, but compared with the hypertensive groups, the normotensive group had higher education and monthly income and lower weight and body mass index. A significant difference was also seen between patients with hypertension stage 1 and those with hypertension stage 2 related to race. Controlled hypertension was observed in about 53.5% of patients in the hypertension stage 1 group and 39.3% in the hypertension stage 2 group.

TABLE 1 Demographic, social, and clinical characteristics of the study participants

Variable	Normotension (n=69)	Hypertension stage 1 (n=83)	Hypertension stage 2 (n=59)	*P* value
Age, y	52.2±13.9	52.1±13.0	51.3±10.1	.917
Men, No. (%)	31 (44.9)	38 (44.2)	26 (46.4)	.971
White race, No. (%)	44 (63.8)	68 (79.1)	32 (57.1)	.021[a]
Married, No. (%)	35 (50.7)	58 (67.4)	30 (56.3)	.176
Weight, kg	74.3±16.2	77.4±14.3	82.9±13.7	.006[b]
Height, m	1.7±0.1	1.6±0.1	1.6±0.1	.497
BMI, kg/m^2	26.7±4.2	28.5±4.6	30.1±4.6	<.001[c]
Education, y	13.0±3.9	11.2±4.3	10.2±4.4	.001[c]
Monthly income, $R[e]	3000.00 (730–15 000)	1950.00 (600–14 000)	1950.00 (500–20 000)	<.028[c]
SBP, mm Hg	121.9±8.3	135.0±13.5	147.5±26.1	<.001[d]
DBP, mm Hg	76.5±6.9	83.1±9.9	90.3±14.5	<.001[d]
Hypertension time, y	–	6.0 (1–33)	10.50 (1–37)	<.001
Drugs, No. (%)	–	1.4 (0.8)	4.0 (1.1)	<.001
Controlled hypertension, No. (%)	–	46 (53.5)	22 (39.3)	<.001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
P value refers to comparisons of the means or proportions among the groups by one-way analysis of variance, Kruskal-Wallis, and Mann-Whitney tests.
[a]Hypertension stage 1 vs hypertension stage 2.
[b]Normotension vs hypertension stage 2.
[c]Normotension vs hypertension stage 1 and hypertension stage 2.
[d]All groups different.
[e]$R (3.3 Real = 1 US$).

3.1 | Arterial proprieties and cognitive performance

The hypertension stage 2 group performed worse than those with normotension and the hypertension stage 1 group in the MoCA and the MMSE. In the neuropsychological evaluation, the group with normotension performed better than the groups with hypertension in the majority of cognitive tests, with significant differences registered mainly between the control and the most severe hypertension group (Table 2). However, after adjustment for educational level, only the following variables retained statistical significance: MoCA (*P*=.030); RAVLT5 (*P*=.031); RAVLTA6 (*P*=.031); VF (*P*<.001); BDST (*P*=.022); FAS (*P*=.021); and DSST (*P*=.025).

Patients in the hypertension stage 2 group had worse structural and functional arterial proprieties compared with the control and hypertension stage 1 group in all arterial proprieties, except for distention, PWV, and AIx75, where the three groups were similar (Table 3).

Table 4 shows cognitive performance considering the cutoff PWV value of 7.90 m/s, which was the mean PWV in patients with hypertension. Individuals with higher PWV had poorer cognitive performance in all cognitive domains, with statistical differences in global cognitive function (*P*=.001), episodic memory (*P*<.001), visuospatial abilities (*P*=.001), attention (*P*=.013), and processing speed (*P*=.001).

On the neuropsychological evaluation considering the patients with hypertension above and under the cutoff mean PWV, language was the most affected domain (21.1% vs 12.5%, *P*=.17), followed by processing speed domain (22.5% vs 5.6%, *P*=.004) and visuospatial abilities domain (15.5% vs 8.3%, *P*=.19). Executive function (8.5% vs 4.2%, *P*=.30) and attention (11.3% vs 1.4%, *P*=.02) were the least affected domains.

3.2 | Correlations between arterial and cognitive variables

Bivariate correlations between the arterial proprieties and cognitive tests in patients with hypertension are presented in Table 5. Functional proprieties (PWV, AIx, AIx75, and central SBP) were more frequently and negatively correlated with cognitive tests, although IMT was the structural propriety that most frequently and negatively correlated with cognitive tests assessing different domains.

Multivariable analysis with arterial proprieties as independent variables and cognitive tests as dependent variables is presented in Table 6. To avoid the collinearity effect between AIx and AIx75 only the AIx was used in the multivariable analysis models. AIx, IMT, and PWV were the variables that more robustly associated with lower cognitive performance in different cognitive domains.

4 | DISCUSSION

The main finding of this study is that higher arterial stiffness in patients with hypertension is associated with worse cognitive performance

TABLE 2 Cognitive performance according to the patient's blood pressure level

Variable, mean±SD	Normotension (n=69)	Hypertension stage 1 (n=83)	Hypertension stage 2 (n=59)	*P* value
MMSE	28.03±1.92	27.43±2.01	26.66±2.07	.001[a]
MoCA	25.58±2.97	24.92±2.87	23.46±3.47	.001[b]
Language				
BNT	0.01±0.99	−0.35±1.27	−0.48±1.19	.045[c]
Memory				
RAVLT5 (sum of 5 trials)	0.02±0.99	−0.05±1.26	−0.65±1.20	.002[b]
RAVLT6	0.03±1.00	−0.21±1.43	−0.71±1.35	.004[a]
RAVLT7	0.05±0.97	−0.13±1.16	−0.50±1.18	.021[a]
REY—30	0.003±1.00	−0.03±1.00	−0.48±0.87	.008[b]
Executive function				
Verbal fluency animal	0.02±1.01	−0.16±0.97	−0.84±0.64	<.001[b]
Backward digit span	0.01±0.99	−0.33±0.93	−0.68±0.76	<.001[b]
TMT-B	0.02±0.98	−0.25±0.85	−0.58±1.19	.007[a]
Phonological verbal fluency	0.04±0.99	−0.31±0.94	−0.71±0.98	<.001[b]
Visuospatial abilities				
REY—C	0.02±0.99	−0.29±1.05	−0.42±1.16	.051
CDT	0.02±0.98	−0.14±1.20	−0.37±1.22	.157
Attention				
Forward digit span	−0.02±1.00	−0.03±0.97	−0.38±0.69	.043[b]
TMT-A	0.08±0.73	−0.41±1.51	0.56±1.04	.005[c]
Processing speed				
Digit symbol substitution test	0.03±0.98	−0.38±0.93	−0.67±0.87	<.001[c]

Abbreviations: BNT, Boston Naming Test; CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test (RAVLT5, sum of 5 recall trials of 15 words; RAVLT6, immediate recall after inference; and RAVLT7, delayed recall after 30 minutes); REY-C, Rey-Osterrieth Complex Figure Test copy; REY-30, Rey-Osterrieth Complex Figure Test delayed recall; SD, standard deviation; TMT-A and TMT-B, Trail Making Test part A and B.

P value refers to comparisons of the means among the groups by the one-way analysis of variance stepwise test with Bonferroni post hoc analysis. All analyses were adjusted to the education level (years of education).

[a]Normotension vs hypertension stage 2.

[b]Hypertension stage 2 vs normotension and hypertension stage 1.

[c]Normotension vs hypertension stage 1 and hypertension stage 2.

across multiple cognitive domains. Language, processing speed, and visuospatial abilities were the most affected cognitive domains and attention was the least affected domain. Both PWV and AIx were the main variables associated with cognitive impairment in the present study. Although AIx and PWV cannot be used interchangeably as an index of arterial stiffness, previous evidence has suggested that the two measures are significantly correlated with each other, yet their impact is slightly different.[34,35]

Elevated PWV has been associated with cognitive impairment in many studies both in young and older adults.[36,37] However, whether hypertension aggravates this association has not been well described. More recently, in the Framingham Heart Study–Third Generation Cohort,[38] investigators explored the cross-sectional associations between carotid-femoral PWV and cognitive function and brain aging in young and middle-aged individuals (mean age, 46 years). In this trial, aortic stiffness was associated with cognitive function and markers of subclinical brain injury in young to middle-aged adults.

McEniery and colleagues[39] have reported that the age-related changes in AIx and aortic PWV are nonlinear, with AIx increasing more in younger individuals, whereas the changes in PWV are more prominent in older individuals. The study populations of Yasmin and Brown[34] and Kelly and colleagues[35] included both younger and older patients, varying widely from the second to the eighth decade. They might thus have found a significant but relatively modest relationship between AIx and PWV. In contrast, the population studied by Lemogoum and colleagues[40] was mainly composed of younger patients, with an average age of 32 years. In our study, patients were mainly middle-aged adults (average age of 52 years), ranging from 25 to 71 years.

TABLE 3 Vessels proprieties according to blood pressure level

Variable, mean±SD	Normotension (n=69)	Hypertension stage 1 (n=83)	Hypertension stage 2 (n=59)	*P* value
Carotid diameter, mm	6.5±0.6	7.0±0.7	7.2±0.8	<.001[b]
Carotid distention, %	4.8±2.1	4.7±2.2	5.0±1.8	.527
Carotid IMT, mm	0.7±0.1	0.8±0.1	0.8±0.1	.005[b]
PWV, m/s	7.5±1.4	7.9±1.2	7.9±1.2	.120
AIx[a]	22.5±12.9	24.1±12.4	30.3±11.9	.001[c]
AIx75[a]	21.2±12.1	23.7±10.1	25.7±9.6	.060
cSBP, mm Hg	111.3±9.5	120.9±15.1	139.1±29.5	<.001[d]
cDBP, mm Hg	76.5±7.8	82.7±10.8	91.8±14.3	<.001[d]

Abbreviations: AIx, augmentation index; AIx75, augmentation index normalized for a heart rate of 75 beats per minute; cDBP, central blood pressure; cSBP, central systolic blood pressure; IMT, intima-media thickness; PWV, pulse wave velocity; SD, standard deviation.
[a]Values adjusted for sex and height.
[b]Normotension vs hypertension stage 1 and hypertension stage 2.
[C]Hypertension stage 2 vs normotension and hypertension stage 1.
[d]All groups different.

In addition, the most intriguing aspect of our study was the discrepancies between AIx and PWV for different aspects of cognitive function. The reasons for such discrepancies are unknown. AIx and PWV are influenced by a number of anatomical and physiological variables. PWV depends on vessel size and the elastic properties of the aortic wall. AIx is determined not only by the amplitude and timing of the reflected pulse wave but also by height, heart rate, left ventricular ejection duration, and BP level.[41,42] The amplitude and timing of the reflected wave depends on PWV and arterial damping, ie, the faster the wave travels or the shorter the distance, the less damping and the greater the amplitude of the reflected wave. Aortic AIx may thus be influenced by many factors including PWV. Sakurai and colleagues[43] also observed that AIx was significantly associated with aging, systolic aortic pressure, heart rate, left ventricular ejection fraction, and height, but PWV was only significantly associated with aging and systolic aortic pressure. Furthermore, AIx gauges the contribution of peripheral wave reflection to the rise in central pulse pressure and is considered a marker of both vascular elasticity and peripheral arterial resistance, closely related with vascular alterations in small arteries including the cerebral bed, which is related to cognitive impairment.[44]

Recently, some studies reported an association between increased arterial stiffness, measured by PWV, and poor cognitive function and suggested that arterial stiffness may be a determinant of cognitive decline and dementia.[11,12] However, the association between central arterial pressure and cognition has received little attention in recent years. Two preliminary studies have shown that higher central pulse pressures are associated with poorer cognition, particularly in the domain of memory recall.[11,45] Pase and colleagues[45] extended these findings by showing that central systolic pressure and pulse pressure amplification are also associated with multiple domains of cognitive performance.

Many processes may explain the higher arterial stiffness and poorer cognitive performance in patients with hypertension, which was worse in the hypertension stage 2 (severe hypertension) group in the present study. Elastic artery stiffening, an age-related process, can be accelerated in the presence of hypertension. Hypertension may produce arterial stiffening by both functional and structural mechanisms.[46]

Young adult patients with hypertension have a "downstream" increase in resistance at the level of the arterioles, causing an "upstream" increase in transmural pressure at the level of the central elastic arteries. This causes weight-bearing elastic lamellae of the large arteries to stretch and become stiffer. Therefore, elevated BP over time can lead to vascular remodeling, hypertrophy, and hyperplasia, structural changes that produce intrinsic arterial stiffening.[47] Thus, it is plausible that both higher PWV and severe hypertension may have an additive effect on cognitive impairment. Similarly, the

TABLE 4 Cognitive performance according to PWV in patients with hypertension

Cognitive domain, mean (SD)	PWV ≤7.9 m/s (n=70)	PWV >7.9 m/s (n=72)	*P* value
MMSE	27.37±1.89	26.86±2.29	.152
MoCA	24.79±3.05	23.83±3.36	.075
Global cognitive function[a]	−0.19±0.57	−0.54±0.72	.001
Language	−0.34±1.12	−0.47±1.35	.550
Memory	0.06±0.96	−0.67±0.95	<.001
Executive function	−0.41±0.62	−0.48±0.74	.548
Visuospatial abilities	−0.18±0.72	−0.40±1.07	.001
Attention	−0.15±0.60	−0.50±1.03	.013
Processing speed	−0.25±0.78	−0.75±0.97	.001

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PWV, pulse wave velocity; SD, standard deviation.
[a]Compound cognitive score was calculated as the mean *z* score of all neuropsychological tests.

TABLE 5 Bivariate correlation between arterial proprieties and cognitive tests at different domains in patients with hypertension

Variable	MMSE		MoCA		GCF		Language		Memory		Executive function		Visuospatial		Attention		Processing speed	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Diameter	.04	.53	−.06	.40	−.18	.01	.05	.45	−.23	.001	−.11	.12	−.07	.26	−.13	.06	−.18	.01
Distension	.03	.62	.04	.55	.18	.01	−.02	.74	.21	.002	.16	.02	.01	.94	.17	.01	.17	.02
IMT	−.08	.27	−.17	.01	−.26	<.001	−.09	.18	−.27	<.001	−.18	.02	−.04	.58	−.22	.001	−.33	<.001
PWV	−.11	.12	−.14	.04	−.30	<.001	−.09	.16	−.32	<.001	−.17	.02	−.14	.05	−.27	<.001	−.28	<.001
AIx	−.24	.001	−.19	.01	−.34	<.001	−.32	<.001	−.18	.01	−.30	<.001	−.23	.001	−.34	<.001	−.27	<.001
AIx75	−.21	.003	−.13	.06	−.29	<.001	−.28	<.001	−.16	.02	−.26	<.001	−.12	.08	−.31	<.001	−.26	<.001
cSBP	−.17	.01	−.24	.001	−.26	<.001	−.14	.05	−.16	.02	−.22	.001	−.21	.003	−.25	<.001	−.20	.003
cDBP	−.07	.23	−.16	.02	−.14	.05	−.01	.94	−.11	.11	−.16	.02	−.09	.19	−.07	.30	−.08	.24

Abbreviations: AIx, augmentation index; AIx75, augmentation index adjusted to 75 beats per minute; BP, blood pressure; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; GCF, global cognitive function; IMT, intima-media thickness; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PWV, pulse wave velocity.

TABLE 6 Multivariable analysis between arterial proprieties as independent variables and cognitive tests as dependent variables in patients with hypertension*

Variable	B	Parameter 95% CI for B	*P* value
		MMSE	
AIx	−0.032	−0.059 to −0.004	.026
		MoCA	
IMT	−4.518	−8.360 to −0.676	.022
		Global cognitive function	
AIx	−0.011	−0.020 to −0.003	.010
IMT	−0.800	−1.562 to −0.038	.040
PWV	−0.141	−0.227 to −0.005	.002
		Language	
AIx	−0.026	−0.042 to −0.010	.001
		Memory	
IMT	−1.659	−2.816 to −0.501	.005
PWV	−0.254	−0.385 to −0.124	<.001
		Executive function	
AIx	−0.015	−0.023 to −0.006	.001
		Visuospatial ability	
AIx	−0.018	−0.030 to −0.006	.004
		Attention	
AIx	−0.017	−0.028 to −0.006	.003
PWV	−0.138	−0.250 to −0.026	.016
		Processing speed	
IMT	−1.774	−2.834 to −0.714	.001
PWV	−0.192	−0.311 to −0.073	.002

Abbreviations: CI, confidence interval; IMT, intima-media thickness; MoCA, Montreal Cognitive Assessment; PWV, pulse wave velocity.

B indicates unstandardized model coefficients that indicate how much the dependent variable varies with an independent variable when all other independent variables are held constant. Consider the effect of augmentation index (AIx) in this example. The unstandardized coefficient, B_1, for AIx is equal to −0.038. This means that for each one-unit increase in AIx, there is a decrease in Mini-Mental State Examination (MMSE) score of 0.032.

*To run the multivariable analysis models, for each dependent variable, all independent variables with *P*<.01 in the bivariate analysis were selected. In models where AIx and AIx adjusted to 75 beats per minute (AIx75) needed to be included, to avoid the collinearity effect, only the AIx was included.

fact that the group with higher PWV (above the study mean) had poorer cognitive performance may be explained by the same processes. Although a PWV cutoff of 7.9 m/s is relatively low, even if it is based on this group, since the usual cutoff is around 10 m/s in assigning high risk on the basis of PWV, it is important to stress that even at this level those patients with higher arterial stiffness had lower cognitive performance.

In the Framingham Heart Study–Third Generation Cohort, although only 18% of the individuals had hypertension, in adjusted regression models, higher carotid-femoral PWV was associated with poorer processing speed and executive function mainly in midlife,

larger lateral ventricular volumes in young adulthood, and a greater burden of white-matter hyperintensity in middle-aged adults.[38]

5 | LIMITATIONS

First, our study used a relatively small sample and is based on a cross-sectional design, and we highlight that an association does not imply causation. Accordingly, our observations need confirmation in longitudinal and adequately powered studies. Second, our study was performed in a select group of patients with hypertension referred to a university hospital, limiting the generalizability of our findings to other populations. Another limitation of this study is the absence of magnetic resonance imaging because we were not able to rule out subclinical cerebrovascular disease, which may determine hypertension impact on these patients. Last, the impact of antihypertensive drugs was not addressed.

6 | CONCLUSIONS

Our data showed that higher arterial stiffness is related to cognitive impairment at different levels of hypertension. In addition, arterial functional (AIx and PWV) and structural (IMT) properties were associated with lower cognitive performance at different domains. Language, processing speed, and visuospatial abilities were the most affected domains. The present findings support the undertaking of further studies to elucidate the mechanisms through which arterial stiffness is associated with cognitive impairment and whether hypertension could have an additive effect on this association.

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CONFLICT OF INTEREST

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