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Measurement of resistance-area product by transcranial Doppler: An alternative tool for cognitive screening in hypertensive on drug treatment?

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ABSTRACT

Introduction: Arterial hypertrophy and remodeling are adaptive responses present in systemic arterial hypertension that can result in silent ischemia and neurodegeneration, compromising brain connections and cognitive performance (CP). However, CP is affected differently over time, so traditional screening methods may become less sensitive in assessing certain cognitive domains. The study aimed to evaluate whether cerebrovascular hemodynamic parameters can serve as a tool for cognitive screening in hypertensive without clinically manifest cognitive decline.

Methods: Participants were allocated into groups: non-hypertensive ($n = 30$) [**group 1**], hypertensive with systolic blood pressure (SBP) < 140 and diastolic blood pressure (DBP) < 90 mmHg ($n = 54$) [**group 2**] and hypertensive with SBP ≥ 140 or DBP ≥ 90 ($n = 31$) [**group 3**]. Measurements of blood pressure and middle cerebral artery blood flow velocity were obtained from digital plethysmography and transcranial Doppler. For the cognitive assessment, the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) and a broad neuropsychological battery were applied.

Results: Patients in groups 2 and 3 show no significant differences in most of the clinical-epidemiological variables or pulsatility index ($p = 0.361$), however compared to group 1 and 2, patients in group 3 had greater resistance-area product [RAP] (1.7 [±0.7] vs. 1.2 [±0.2], $p < 0.001$). There was a negative correlation between RAP, episodic memory ($r = -0.277$, $p = 0.004$) and cognitive processing speed ($r = -0.319$, $p = 0.001$).

Conclusion: RAP reflects the real cerebrovascular resistance, regardless of the direct action of antihypertensive on the microcirculation, and seems to be a potential alternative tool for cognitive screening in hypertensive.

Abbreviations list: AD, Alzheimer's Disease; ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptors Blocker; AHD, Antihypertensive Drugs; ARI, Autoregulation Index; BP, Blood Pressure; BNT, Boston Naming Test; BHI, Breath-Holding Index; BHT, Breath-Holding Test; CA, Cerebral Autoregulation; CBF, Cerebral Blood Flow; CBFV, Cerebral Blood Flow Velocity; CVR, Cerebrovascular Resistence; CDT, Clock Drawing Test; CP, Cognitive Performance; CrCP, Critical Closing Pressure; DBP, Diastolic Blood Pressure; MRI, Magnetic Resonance Imaging; MCA, Middle Cerebral Artery; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; PI, Pulsatility Index; PP, Pulse Pressure; PWV, Pulse Wave Velocity; RAP, Resistance–Area Product; RAVL, Rey Auditory-Verbal Learning Test; REY, Rey Complex Figure Test; AH, Systemic Arterial Hypertension; SBP, Systolic Blood Pressure; TMT, Trail Making Test; TCD, Transcranial Doppler; WAIS-III, Wechsler Intelligence Scale For Adults; WMH, White Matter Hyperintensity.

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1. Introduction

Systemic arterial hypertension (AH) is an important risk factor for chronic subcortical arteriopathy or small penetrating artery disease [1]. Brain tissue is more vulnerable because its microcirculation has low impedance, allowing an increase in pulse wave velocity (PWV) and pulse pressure (PP), are transmitted along the length of this microcirculation [2–4]. The resulting microvascular damage can be observed radiologically on magnetic resonance imaging (MRI), with T2-weighted images, such as white matter hyperintensities (WMH), microbleeds and/or lacunar infarcts, which is part of the radiological spectrum of small penetrating artery disease [5].

The WMH pattern diffusely involves deep white matter and periventricular regions (internal vascular border areas), where perfusion pressure is lower, making them more susceptible to chronic hypoperfusion [5]. There is consistent evidence that the severity of this radiological change is associated with global cognitive function, but it is preceded by several mechanisms [6–8], so that the cognitive abilities of hypertensive patients are affected differently over time, which influences their cognitive performance (CP) in an initial assessment and/or the speed of progression of long-term cognitive decline [9,10]. As a result, depending on the severity and duration of the disease, traditional screening methods [11,12] may become less sensitive in identifying dysfunctions in certain cognitive domains.

Physiological measures independent of cognitive assessment are presented as an alternative tool for detecting cognitive decline. Hemodynamic changes such as increased pulsatility index (PI) and reductions in cerebral blood flow velocities (CBFV) are found in patients with Alzheimer's Disease (AD) and in these patients reduced cerebrovascular reactivity in the middle cerebral artery (MCA) appears to be a predictor of faster cognitive decline [13]. Likewise, other hemodynamic parameters have been shown to be directly related to clinically manifest cognitive decline [14].

We hypothesized that also in the preclinical phase of cognitive impairment, hypertensive patients should present cerebral hemodynamic parameters, independent of potential mechanisms of direct action of antihypertensive drugs (AHD) on the vascular bed, which correlate with their CP.

As result, the present study aimed to assess whether hemodynamic parameters, measured by transcranial Doppler (TCD), can serve as an alternative tool for cognitive screening in hypertensive on drug treatment.

2. Methods

2.1. Study design

From a prospective data collection carried out between June 2013 and December 2015, the clinical-epidemiological characteristics, cognitive performance, cerebral and systemic hemodynamic parameters of 226 individuals were analyzed. Hypertensive patients were recruited from the hypertension outpatient clinic, of the Instituto do Coração (INCOR) of the Hospital das Clínicas, University of São Paulo Medical School (Brazil), while non-hypertensive volunteers were recruited from the institution's general outpatient clinics or from the own academic Community, usually by direct invitation. The study was approved by institutional Research Ethics Committee and all participants gave written informed consent.

We collect demographic and clinical-epidemiological data of each participant through the directed anamnesis. Participants with one or more of the following conditions were excluded: stroke, clinically manifest cognitive decline, diabetes mellitus, carotid artery stenosis greater than or equal to 50 % (estimated by cervical Doppler US), heart failure with EF $<$ 35 %, atrial fibrillation, known neurodegenerative and/or psychiatric disease, epilepsy and/or use of anticonvulsant medications.

The mean resulting from the levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mmHg, CBFV (to be described then) and the number of AHD were used to divide the sample into three groups according to the following criteria, adapted from Serrador et al [15].: **a)** Group 1 (non-hypertensive volunteers): formed by those with SBP $<$ 140 and DBP $<$ 90; **b)** Group 2: hypertensive patients on AHD with SBP $<$ 140 and DBP $<$ 90; **c)** Group 3: hypertensive patients on AHD with SBP $\geq$ 140 or DBP $\geq$ 90.

The definition of AH followed the Brazilian guidelines on hypertension valid at the time of the study [16].

2.2. Cerebral hemodynamic parameters

TCD was performed in a room with controlled temperature (~25 °C) and minimal external noise, and the patient was kept in the supine position with the head elevated to 30° To measure the CBFV of the MCA, the transtemporal windows were kept under manual insonation for 3 min, one side at a time, at a depth of 50 $\pm$ 5 mm, using a 2-MHz transducer (DWL, Doppler-BoxX, Germany). The BP was continuously recorded noninvasively by digital plethysmography (Finometer™, Finapres Medical Systems BV, Netherlands), with the arm kept at the same level in relation to the body for placement of the cuff on the middle finger or index finger of the left hand. Recording was only started after matching the plethysmography values with the manual BP measurement. The mean SBP and DBP values obtained during this recording period were used to later allocate the patients to the different study groups.

The simultaneous measurements of CBFV and BP were estimated beat-to-beat using a linear regression analysis. All signals were visually inspected to identify artifacts or noise and the frequency of 20 Hz was used as a cut-off to filter the signals. The calculation of critical closing pressure (CrCP) and resistance-area product (RAP) values were performed according to previous publications [17,18]. In brief, the intercept with the BP axis, indicates the value of BP at which cerebral blood flow (CBF) becomes zero, corresponds to CrCP. The perfusion pressure is equal to the product of flow volume and vascular resistance and the absolute flow volume across a vessel is equal to the product of mean velocity and the cross-sectional area. Therefore, the inverse of the slope of the regression line was a measure of vascular resistance and cross sectional area, which correspond to RAP. PI were calculated using the formula [(systolic CBFV) – (diastolic CBFV)]/ (mean CBFV). All these hemodynamic parameters were evaluated offline, in an automated way, using a specific software (Department of Cardiovascular Sciences, University of Leicester, UK) that processed the recording of the simultaneous records of CBFV and BP, stored on the computer.

Patients were excluded due to technical problems, such as the absence of an insonation window or Finometer malfunction. Patients whose records became unusable after the computerized analysis and those diagnosed with hypertension during the continuous BP recording period were also excluded.

Cerebral autoregulation (CA) was evaluated using spontaneous fluctuations in mean BP as the input and changes in CBFV as the output. The autoregulation index (ARI) was calculated through the appropriate step response profile, corresponding to one of the 10 existing curve models. Each curve corresponds to an ARI value, ranging from 0 (absence of CA) to 9 (best existing CA response) [19]. To obtain the Breath-holding index (BHI), the breath-holding test (BHT) was performed [20]. In brief, the MCA CBFV is measured during a period of normal breathing in ambient air for about 4 min; then, patients are instructed to hold their breath for 30 s, while the MCA CBFV is continuously recorded in order to document the highest mean velocity at the end of the apnea period.

Thus, the BHI was calculated as the percentage increase in MCA CBFV recorded during apnea, divided by the apnea time in seconds ($[CBFV(f) - CBFV(i)/ CBFV(i)] \times 100 \times s^{-1}$), where **CBFV(f)** is the mean velocity of the apnea, **CBFV(i)** is the mean velocity of the normal

breathing and s^{-1} denotes per second of apnea. When the BHI result is less than 1.12, the cerebrovascular reactivity is considered compromised and if less than or equal to 0.69, it is considered exhausted.

2.3. Cognitive assessment

It was made by one of the three neuropsychologists (N.C.M; C.M.M; M.S.Y.) participating in the study, on different days from those on which the measurements of systemic and cerebral hemodynamic parameters were carried out. The Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) and a large neuropsychological battery, prepared in accordance with the recommendations of the National Institute of Neurological Disorders and Stroke – Canadian Stroke Network [21], were applied to studies interested in evaluating cognitive alterations in patients with cerebrovascular diseases and the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology [22].

The MMSE is a commonly used 30-point scale for assessing cognitive function based on orientation, registration, attention and calculation, recall, language, and praxis. Because participants had heterogeneous educational levels, scores were adjusted for level of education. The following cutoff scores were used to identify abnormal cognition in this study: ≤ 21 for patients with < 8 years of education, ≤ 23 for those with 9–11 years of education, and ≤ 25 for those with ≥ 12 years of education [23].

The MoCA is a rapid screening instrument to identify mild cognitive impairment (MCI). It assesses attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points. A previous validation study in Brazil suggested ≤ 25 points as the ideal cutoff for MCI identification [24].

Among the cognitive domains, episodic memory was assessed using the Rey Auditory-Verbal Learning Test (RAVLT 1–5 and late-RAVLT) and the Rey Complex Figure Test drawing (late-REY); language, through the Boston Naming Test (BNT); attention, through repetition of the digits of the Wechsler Intelligence Scale for adults (WAIS-III) in the direct order and the Trail Making Test part A (TMT-A); cognitive processing speed, by copying the WAIS-III scale codes; praxis, through the copy of the Rey Complex Figure Test (copy-REY) and the Clock Drawing Test (CDT); and the executive function, through the repetition of the WAIS-III scale digits in inverse order and the Trail Making Test part B (TMT-B).

For the purpose of analyzing cognitive function, the raw values of performance in neuropsychological tests were transformed into z-scores. Thus, a composite score was made for executive functions (average z-score between semantic fluence verbal, TMT-B, inverse digits), praxis (average z-score between CDT, REY-copy), attention (average z-score between TMT-A, digits rights), episodic memory (mean z score between RAVLT [A1-A5], RAVLT-late, REY-late), language (BNT), cognitive processing speed (WAIS-III scale codes copy). The domain was considered compromised if it presented a z-score below -1.5 SD of the mean, using the normotensive group as a reference.

2.4. Statistical analysis

The *Kolmogorov–Smirnov* test was used to assess the probability distribution of the quantitative parameters and guided the hypothesis tests. The evaluation of the distribution of qualitative variables according to the groups of controlled hypertensives, uncontrolled hypertensives and normotensives was performed using *Fischer's exact* test. The *Kruskal-Wallis* test was applied to compare the quantitative data between the three study groups, with *post-hoc Bonferroni* analysis. When the comparison of interest was between the two groups of hypertensive patients, controlled or uncontrolled, the *Mann-Whitney* test was used. And to evaluate the correlation between the quantitative data, the *Spearman* correlation test was applied.

All tests took into account a bidirectional α of 0.05 and a confidence interval (CI) of 95 % and were performed with the computational support of software R (https://www.r-project.org/), IBM SPSS 25 (Statistical Package for the Social Sciences) and Excel 2016 ® (Microsoft Office).

3. Results

Between June 2013 and December 2015, 226 (151 hypertensive on AHD and 75 non-hypertensive) volunteers consented to participate in the study. Among hypertensive patients, 16 were excluded due to technical problems (15 because they did not have an insonation window and one due to Finomiter™ malfunction) and 50 because they had unusable records after computerized analysis by the software (e.g., patient motion artifacts, delay in simultaneous BP-CBFV recording generating gaps in software readings). Among the non-hypertensive individuals, 32 were excluded due to unusable records, five had criteria for the diagnosis of AH and eight had technical problems (Fig. 1).

Compared to group 1, patients in group 3 were older (51 ± 12 years), obese (BMI 26.9 [±4.4] vs. 30.5 [±4.5], $p = 0.007$) and had lower educational level (education [years], 9 [±5] vs. 12 [±4], $p = 0.029$) that are known factors that correlate with treatment unsuccess, however neither these nor other clinical-epidemiological variables differed between the two hypertensive groups.

The mean time and number of AHD used for treatment were similar between the groups 2 and 3, however the use of angiotensin converting enzyme inhibitor (ACEI) was higher among patients in group 2 (46.3 % vs. 19.4%), whereas angiotensin receptors blocker (ARB) was the most prevalent class among patients in group 3 (33.3 % vs. 64.15%), both differences were statistically significant (Table 1).

The CP of the groups studied is shown in Tables 2 and 3.

Regarding specific neuropsychological tests, only those used to assess executive functions showed some statistically significant difference, but unlike what was observed after applying the scale digits in reverse order, in which both groups of hypertensive individuals had worse results, performance in the semantic verbal fluency was lower only among controlled hypertensives, compared to normotensives ($p = 0.035$).

Nevertheless, the composite score resulting from these tests did not show significant impairment of the executive functions of any of the hypertensive groups, unlike what was observed with the composite scores of the tests that assessed episodic memory (78 [±37] vs. 61 [±18], respectively, group 1 vs. group 2, $p = 0.014$) and language (54 [±7] vs. 48 [±13], respectively, group 1 vs. group 2 or 3, $p = 0.003$).

Table 4 presents the correlation between cerebrovascular hemodynamic parameters and performance according to MMSE, MoCA and specific cognitive domains of hypertensive patients. The negative correlation between the stiffness of small cerebral arteries (expressed by RAP) with episodic memory ($r = -0.277$, $p = 0.004$) and cognitive processing speed ($r = -0.319$, $p = 0.001$) stands out.

There was a trend towards a reduction in PI with the use of most AHD, but this positive effect was more significant with the use α-agonists ($p = 0.009$). No other cerebrovascular hemodynamic parameters were modified by AHD (Table 5).

4. Discussion

In the chronic phase of the AH, additional changes on the arterial wall occur that include the accumulation of fibrous proteins, elastin and collagen and degeneration of smooth muscle cells, so that this chain of pathophysiological events, associated with other mechanisms, results in ischemia (often silent) and neurodegeneration [25–27].

These silent ischemia, when involving the white matter, affect the connections between the prefrontal cortex and the deep subcortical nuclei, and may interrupt the connectivity between these regions and cause altered functioning of the frontal lobes and executive dysfunctions

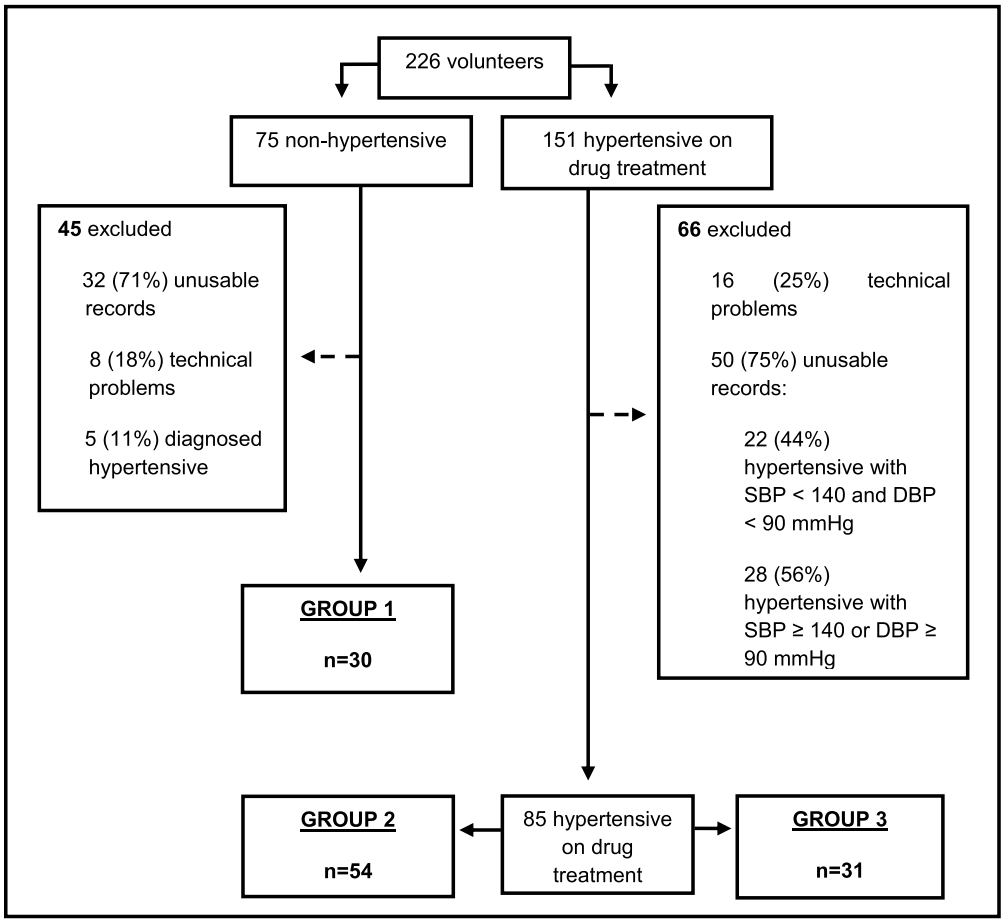

Fig. 1. Enrollment of patients.

[28], but the cognitive abilities of hypertensive patients are affected differently over time, which influences their CP in an initial assessment [9,10].

However, despite the same treatment time (mean, 9 years), we observed that only patients in group 2 had significantly lower verbal fluency compared to normotensives. This was an unexpected result, since the relationship between good cognitive performance and effective BP control would be intuitive. It is possible that this was due only to the difference between the number of participants between groups 2 and 3; on the other hand, given the existing difference between the AHD most used by this groups, future research may help to understand whether the way in which the renin-angiotensin-aldosterone system is modulated can also influence the CP of hypertensives.

Physiological measures independent of cognitive assessment may be an additional alternative tool for screening cognitive. CBFV is decreased in patients with various degrees of cognitive impairment, and values lower than 39.1 cm/s can be predictive of different stages of this clinical condition [29], while PI and cerebrovascular resistence (CVR) can be considered independent factors for predicting cognitive deterioration and progression to AD [30]. Likewise, other publications on changes in cerebral hemodynamic status and cognitive functions evaluated patients with overt dementia [31,32], which makes it difficult to interpret the early role of vascular risk factors and their concomitant cerebral hemodynamic changes in the development of cognitive decline.

Unlike the others, the present study was the first to evaluate the association between cerebral hemodynamic parameters and CP in hypertensives without clinical manifestations of cognitive impairment. Reflecting the status of the chronic alteration in the tunica-media/intima ratio (and the consequent arterial stiffness) resulting from AH, the RAP (Table 4) showed to be a useful hemodynamic parameter for cognitive screening in middle-aged hypertensive patients, especially those related to frontoparietal network [33].

It is important to highlight that although the definition of the groups was based on a single BP measurement, the significant increase in RAP ($1.6 \pm [1.3–1.9]$, $p < 0.001$) in the patients in group 3 suggests that possibly these individuals, in fact, had been long-time poor BP control. Furthermore, patients in groups 2 and 3 show no significant differences in most of the clinical-epidemiological variables evaluated in the study, so that, except for the type of AHD and/or BP control, it seems unlikely that any of these variables could have influenced the result of the cognitive evaluation of these patients.

As a result of the increase in RAP, similar to what happens with normal aging, cerebral arterioles do not have the same elasticity to attenuate the PP generated by the left ventricle, which ends up being transmitted entirely through its wall and to the perivascular brain tissue, resulting in secondary damage (e.g., microbleeds, silent ischemia), a phenomenon known as pulse-induced encephalopathy, which is related to progressive cognitive decline [34]. It is possible that this phenomenon is one of the main pathophysiological mechanisms in the pre-clinical stages of cognitive decline in hypertensive patients, especially in those with poor BP control, since they do not have impaired CA or lower CBFV, but they maintain a significant increase in RAP, as presented in more detail in our previous publication [35].

On the other hand, in the present study, the usual associations between PI and BHI that were once directly related to cognitive decline [14] were not observed. Patients in group 3 showed a general tendency to reduce PI, which was more significant with the use of diuretics, β-blockers and α2-agonists. As these and other AHD can reduce vascular

Table 1
Sociodemographic and clinical characteristics.

	GROUP 1 (n = 30)	GROUP 2 (n = 54)	GROUP 3 (n = 31)	p value
Sex. female (n°,%)	12(40%)	22(40.7%)	20(64.5%)	0.073
Age (years), mean ± SD	43(±11)	51(±12)	51(±12)	**0.013**[a]
Education (years), mean ± SD	12(±4)	10(±5)	9(±5)	**0.029**[b]
Height (m), mean ± SD	1.7(±0.1)	1.7(±0.1)	1.6(±0.1)	**0.007**[b]
BMI (Kg/m^2), mean ± SD	26.9(±4.4)	27.7(±8.4)	30.5(±4.5)	**0.007**[b]
MBP (mmHg), mean ± SD	80.8(±10.1)	82.8(±14.3)	102.8 (±15.2)	**<0.001**[c]
Treatment time (years), mean ± SD	–	9(±7)	9(±8)	0.489
Most used drugs				
ACEI (n°,%)	–	25(46.3%)	6(19.4%)	**0.011**
ARB (n°,%)	–	18(33.3%)	20(64.5%)	**0.005**
CCB (n°,%)	–	20(37.0%)	13(41.9%)	0.413
BB (n°,%)	–	18(33.3%)	11(35.5%)	0.512
VASODIL (n°,%)	–	2(3.7%)	1(3.2%)	0.700
DIURETIC (n°,%)	–	36(66.7%)	18(58.1%)	0.287
α2-AGONIST (n°,%)	–	5(9.3%)	4(12.9%)	0.427
ALDOST-A (n°,%)	–	7(13.0%)	5(16.1%)	0.460
Total number of drugs	–	2(±2)	3(±2)	0.646

NOTE: Group 1: Non-hypertensives; Group 2: Hypertensive with SBP < 140 and DBP < 90 mmHg; Group 3: Hypertensive with SBP ≥ 140 or DBP ≥ 90 mmHg; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MBP: Mean Blood Pressure; BMI: Body Mass Index; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin I Receptor Blocker; CCB: Calcium Channel Blocker; BB: β1-Adrenergic Receptor Blocker; VASODIL: Vasodilators; α2-AGONIST: α−2 Adrenergic Receptor Agonist; ALDOST-A: Aldosterone antagonist.
p values based on *Fischer's exact* test. *Kruskal-Wallis* or *Mann-Whitney* test.
[a] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 2 or group 3.
[b] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 3.
[c] significant *post hoc* comparisons ($p < 0.05$): group 1 and group 2 vs. group 3.

Table 2
Performance on neuropsychological tests used in cognitive assessment.

	GROUP 1 (n = 30)	GROUP 2 (n = 54)	GROUP 3 (n = 31)	p value
Global Cognition				
MMSE	28(±2)	28(±2)	28(±2)	0.180
MoCA	26(±3)	24(±3)	25(±4)	**0.047**[a]
Episodic Memory				
RAVLT (A1-A5)	43(±11)	37(±14)	38(±18)	0.182
Late - RAVLT	11(±4)	10(±4)	10(±5)	0.845
Late - REY	21.7(±34.3)	11.6(±7.9)	12.5(±9.9)	0.098
Attention				
TMT -A (s)	49(±28)	61(±38)	58(±50)	0.262
Direct Digits	7(±3)	6(±3)	5(±5)	0.064
Praxis				
CDT	4(±1)	4(±2)	4(±2)	0.329
Copy - REY	29.9(±9.4)	28.2(±10.2)	27.5(±13.0)	0.570
Executive Functions				
Semantic VF	18(±6)	15(±6)	15(±8)	**0.035**[a]
TMT -B (s)	122(±80)	123(±93)	112(±127)	0.485
Inverse Digits	6(±8)	3(±2)	3(±3)	**0.006**[b]

NOTE: Group 1: Non-hypertensives; Group 2: Hypertensive with SBP < 140 and DBP < 90 mmHg; Group 3: Hypertensive with SBP ≥ 140 or DBP ≥ 90 mmHg; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; RAVLT A1-A5: sum of the five evocations of Rey Auditory-Verbal Learning Test; Late-RAVLT: Late recall of Rey Auditory-Verbal Learning Test; Late-REY: Evocation after 30 min of the Rey Complex Figure Test; Direct Digits: Wechsler Adult Intelligence Scale-III Direct Digits Subtest; TMT-A: Trail Making Test runtime (seconds) part A; CDT: Clock Drawing Test corrected by Shulman score; Copy-REY: the copy of the Rey Complex Figure Test; TMT-B: Test runtime (seconds) of Trail Making Test part B; Inverse Digits: Inverse Digits Subtest of the Wechsler Adult Intelligence Scale-III; Semantic VF: Semantic Verbal Fluency animals.
p values based on the *Kruskal-Wallis* test and *Fischer's exact* test.
[a] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 2.
[b] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 2 and group 3.

Table 3
Performance on neuropsychological tests grouped according to specific cognitive domains.

	GROUP 1 (n = 30)	GROUP 2 (n = 54)	GROUP 3 (n = 31)	p value
Episodic Memory, mean ± SD	78(±37)	61(±18)	69(±20)	**0.014**[a]
Cognitive Impairment (n°,%)	0(0.0%)	4(7.7%)	1(3.7%)	0.506
Language, mean ±SD	54(±7)	48(±13)	48(±13)	**0.003**[b]
Cognitive Impairment (n°,%)	1(3.4%)	3(5.8%)	3(11.1%)	0.531
Cognitive Processing Speed, mean ±SD	52(±22)	42(±23)	52(±21)	0.050
Cognitive Impairment (n°,%)	2(6.9%)	8 (15.4%)	2(7.4%)	0.487
Attention, mean ±SD	58(±26)	69(±37)	73(±47)	0.276
Cognitive Impairment (n°,%)	0(0.0%)	2(3.8%)	0(0.0%)	0.496
Praxis, mean ±SD	35(±8)	33(±9)	36(±9)	0.173
Cognitive Impairment (n°,%)	3 (10.3%)	6 (11.5%)	2(7.4%)	0.919
Executive Functions, mean ±SD	151 (±76)	146 (±90)	149 (±126)	0.817
Cognitive Impairment (n°,%)	1(3.4%)	5(9.6%)	3(11.1%)	0.551

NOTE: Group 1: Non-hypertensives; Group 2: Hypertensive with SBP < 140 and DBP < 90 mmHg; Group 3: Hypertensive with SBP ≥ 140 or DBP ≥ 90 mmHg; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment. The cognitive domain was considered compromised if it presented a z-score < −1.5 SD of the mean. using the normotensive group as a reference.
p values based on the *Kruskal-Wallis* test and *Fischer's exact* test.
[a] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 2.
[b] significant *post hoc* comparisons ($p < 0.05$): group 1 vs. group 2 and 3.

resistance by direct action [36–38], RAP would have an advantage over PI as an independent cerebrovascular parameter for screening cognitive in individuals on drug treatment, because it is related to chronic adaptive cerebrovascular changes (reflecting the real CVR) and, unlike PI, it is less influenced by direct action of some AHD.

Regarding BHI, despite the significant impairment observed in the hypertensive patients in the sample ($p = 0.008$), it did not prove to be a sensitive neurosonological parameter in screening cognitive. Here, hypertensive patients were separated into groups according to the average of their BP levels obtained throughout the entire period of continuous monitoring with the TCD, so that some of these patients, despite all methodological care, may have shown greater fluctuations of the BP during the exam. If BP is elevated in the course of hypercapnia (necessary for the calculation of BHI), CVR also increases, which may contribute to blunted CO2-associated vasodilation [15]. Thus, in individuals with high BP, BHI may have a low positive predictive value for identifying early stages of cognitive decline in hypertensive patients.

We believe that the methodology adopted in the present study can be used outside the search context, as the TCD and Finometer™ are portable devices and once the CBFV and BP records are carried out, the data are processed in a fully automated way. Its use can be a useful tool as part of routine follow-up exams of hypertensive, as it would allow preselecting them for a broader neuropsychological assessment.

Further studies are needed to identify which RAP cut-off is more sensitive for cognitive screening and, above all, what would be the best therapeutic approach for these patients, given that they would not yet have clinically manifest cognitive decline.

The study has important limitations: 1) Groups were not size equal to be compared and there may have been patients with occult cerebrovascular disease, since they did not undergo neuroradiological evaluation. There is consistent evidence that the severity of WHM correlates with and can modify CVR [39]; 2) AH is related to other conditions such as sedentary lifestyle, unhealthy eating habits and

Table 4
Correlation between cerebrovascular hemodynamic parameters and performance according to MMSE, MoCA and cognitive domains of hypertensive groups.

	CBFV	CrCP	RAP	BHI	PI
MEEM					
r	0.215	0.053	0.182	0.017	−0.032
p value	**0.032**	0.601	0.071	0.864	0.755
MoCA					
r	0.210	0.077	0.167	0.033	0.111
p value	**0.037**	0.446	0.099	0.748	0.275
Episodic Memory					
r	0.201	0.03	−0.277	−0.045	−0.048
p value	**0.037**	0.754	**0.004**	0.647	0.624
Language					
r	−0.151	0.095	0.120	0.094	−0.068
p value	0.120	0.330	0.215	0.334	0.484
Cognitive Processing Speed					
r	−0.177	0.014	−0.319	−0.041	−0.011
p value	0.067	0.886	**0.001**	0.672	0.908
Attention					
r	0.004	−0.068	−0.081	−0.047	0.072
p value	0.969	0.486	0.403	0.626	0.459
Praxis					
r	−0.045	0.025	0.038	0.105	−0.017
p value	0.647	0.798	0.695	0.281	0.860
Executive Functions					
r	0.019	0.240	−0.115	−0.089	0.189
p value	0.843	0.112	0.236	0.358	0.051

NOTE: MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; CBFV (cm/s): Cerebral Blood Flow Velocity; CrCP: Critical Closing Pressure; BHI: Breath Holding Index; RAP: Area-Resistance Product; PI: Pulsatility Index.
p values and correlation estimates based on *Spearman's* correlation coefficient.

dyslipidemia that are associated with cognitive decline [40] were not controlled, so that it is not possible to measure how much these variables may have influenced the result of the CP of the hypertensive patients; 3) Due to its observational design, frequently combined use of AHD and the absence of a control group of untreated hypertensive, it was not possible to evaluate the potential influence of AHD on all cerebral hemodynamic parameters analyzed, nor how long it would take for the treatment to promote changes in these parameters, as this could impact RAP sensitivity for cognitive screening.

5. Conclusion

Preclinical alterations in episodic memory and cognitive processing speed in hypertensive patients can be identified early through the measurement of RAP by TCD, which reflects the real CVR, regardless of the use of AHD with direct action on the cerebrovascular bed. TCD is an inexpensive method and seems to be a potential alternative tool for screening for a broader neuropsychological assessment in hypertensive on AHD treatment.

Additional studies are needed to assess whether monitoring the status of the tunica-media/intima relationship by measuring the RAP can also be used as a parameter of the long-term response to AHD treatment and the cognitive prognosis of these patients.

Compliance with ethical standards

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Table 5
Distribution of cerebrovascular hemodynamic parameters according to the most used antihypertensive drug class.

	GROUP 2 mean (±SD)	GROUP 3 mean (±SD)	p value
ACEI			
CBFV	60.5(±12.9)	57.2(±14.1)	0.174
CrCP	10.6(±13.8)	10.2(±10.9)	0.819
RAP	1.3(±0.4)	1.5(±0.6)	0.135
BHI	1.0(±0.5)	1.2(±0.6)	0.347
PI	0.7(±0.1)	0.7(±0.2)	0.554
ARB			
CBFV	57.4(±15.1)	59.3(±12.5)	0.353
CrCP	10.0(±11.0)	10.7(±12.8)	0.530
RAP	1.5(±0.7)	1.4(±0.4)	0.437
BHI	1.1(±0.6)	1.1(±0.6)	0.750
PI	0.7(±0.2)	0.7(±0.2)	0.144
CCB			
CBFV	55.4(±13.6)	60.3(±13.5)	0.123
CrCP	9.2(±12.4)	11.1(±11.7)	0.379
RAP	1.6(±0.5)	1.4(±0.6)	0.114
BHI	1.1(±0.6)	1.1(±0.6)	0.537
PI	0.7(±0.1)	0.7(±0.2)	0.879
BB			
CBFV	56.9(±13.1)	59.2(±14.0)	0.528
CrCP	8.1(±9.2)	11.6(±13.0)	0.319
RAP	1.5(±0.5)	1.5(±0.6)	0.911
BHI	1.1(±0.5)	1.1(±0.6)	0.878
PI	0.7(±0.1)	0.7(±0.2)	**0.043**
DIURETICS			
CBFV	58.5(±14.4)	58.3(±12.5)	0.827
CrCP	8.9(±10.2)	13.0(±14.3)	0.244
RAP	1.4(±0.5)	1.5(±0.7)	0.320
BHI	1.1(±0.6)	1.2(±0.6)	0.309
PI	0.7(±0.1)	0.7(±0.3)	**0.047**
α2- AGONIST			
CBFV	63.2(±8.1)	57.9(±14.1)	0.194
CrCP	5.4(±4.1)	11.0(±12.4)	0.493
RAP	1.4(±0.3)	1.5(±0.6)	0.637
BHI	0.9(±0.4)	1.1(±0.6)	0.247
PI	0.8(±0.1)	0.7(±0.2)	**0.009**

NOTE: Group 2 ($n = 54$): Hypertensive with SBP < 140 and DBP < 90 mmHg; Group 3 ($n = 31$): Hypertensive with SBP ≥ 140 or DBP ≥ 90 mmHg; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin I Receptor Blocker; CCB: Calcium Channel Blocker; BB: β1-Adrenergic Receptor Blocker; α2-AGONIST: α−2 Adrenergic Receptor Agonist; CBFV (cm/s): Cerebral Blood Flow Velocity; CrCP: Critical Closing Pressure; BHI: Breath Holding Index; RAP: Area-Resistance Product; PI: Pulsatility Index.
p value based on the *Mann-Whitney* test.

Consent for publication

The subjects gave informed consent.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethical approval

The study was approved by the Research Ethics Committee (CONEP - Plataforma Brasil) linked to the Ministry of Health (CAAE: 10637712.4.0000.0068) and by Ethics Committee for Analysis of Research Projects (CAPPesq) of INCOR.

CRediT authorship contribution statement

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Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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