HHS Public Access

Author manuscript

Cerebrovasc Dis. Author manuscript; available in PMC 2015 August 20.

Published in final edited form as:

Cerebrovasc Dis. 2014 ; 38(1): 10–16. doi:10.1159/000365349.

Assessment of cerebrovascular reactivity during resting state breathing and its correlation with cognitive function in hypertension

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Abstract

Background—Hypertension is associated with cognitive deficits, particularly executive function, and decreased cerebral microvascular responsiveness to CO_2 (CO_2 vasoreactivity). The relation between CO_2 vasoreactivity and executive function is not known. Protocols to assess CO_2 vasoreactivity are cumbersome and require inhaling a CO_2-enriched gas. We explored the ability to measure CO_2 vasoreactivity using end-tidal CO_2 fluctuations during normal breathing and the association of this measure with cognitive function in hypertension.

Methods—Executive function (Trail Making Test Parts A/B), memory, attention and blood flow velocity (BFV) in the middle cerebral artery using Transcranial Doppler were measured in hypertensive subjects who were tapered-off their treatment for 3 weeks. BFV was measured while sitting normally breathing for 5 minutes followed by breathing 5% CO_2 gas and hyperventilation for 2 minutes each. We calculated CO_2 vasoreactivity as the rate of BFV change from hypoventilation to hyperventilation, and as a modelderived measure using the normal breathing data. The latter was derived using nonlinear Principal Dynamic Modes (PDM) which modelled the dynamic effect of fluctuations in end-tidal CO_2 and blood pressure upon BFV during normal room-air respiration. Multiple regression analyses were used to correlate cerebral hemodynamics with cognitive measures.

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Authors' contribution: Conception and design of this analysis: IH, VM, DC, HC; Data collection: IH; Modeling and derivation of modeling measures: VM, DC; Drafting the article or revising it critically for important intellectual content: IH, VM, HC

Competing interests: NONE

Results—Data were collected from 41 individuals with hypertension (mean age=71 years, 24% African Americans, 61% women, off antihypertensive therapy). Lower CO_2 vasoreactivity was associated with worse executive function test score using both calculation methods: p-value using the hyper/hypoventilation data was 0.04 and from PDM analysis was 0.009. PDM calculations showed a stronger correlation with executive function (correlation=0.41 vs 0.21 using the hyper/hypoventilation data). There were no associations with memory or attention measures. There was a weak but statistically significant correlation between the two calculation methods of CO_2 vasoreactivity (r^2=14%, p=0.02).

Conclusion—This study suggests that, in hypertension, the decrease in CO_2 vasoreactivity is associated with lower executive function. This may offer new insight into the vascular underpinning of cognitive decline in hypertension. We demonstrate that calculating CO_2 vasoreactivity is possible during normal breathing. If replicated in future studies, this may offer a more convenient clinical way to assess CO_2 vasoreactivity in hypertension and cognitive disorders.

Keywords

hypertension cerebral blood flow

Introduction

Hypertension leads to cognitive impairment and dementia.[1] Early on, hypertension is commonly associated with a decline in executive function that may predict future cognitive and functional loss.[2,3] It is suggested that this association is related to its effect on the microvasculature of the brain. Hypertension is also associated with decreased responsiveness to carbon dioxide (CO_2)[4] which may be an early marker of microvascular dysfunction and impaired endothelial health.[5] We therefore hypothesized that lower CO_2 vasoreactivity in hypertension is associated with lower executive function. To our knowledge, no prior study has explored this association in hypertensive individuals.

In healthy individuals, cerebral blood flow is tightly regulated to meet the metabolic demands of the brain. The ability to maintain this metabolic demand can be assessed using Transcranial Doppler. Two main indicators of cerebral hemodynamics have been commonly measured: (i) the ability to maintain cerebral blood flow velocity (BFV) during fluctuating perfusion pressure (autoregulation) and (ii) alterations in BFV due to arteriolar constriction or dilatation triggered by fluctuating end-tidal CO_2 (CO_2-vasoreactivity). Hypertension and aging are associated with decreased CO_2-vasoreactivity but relatively preserved autoregulation. [6-8] Lower CO_2-vasoreactivity is linked to an increased risk of vascular brain injury and death.[9,10]

Artificial changes in systemic blood pressure can be induced by standing. End-tidal CO_2 can be induced by breath holding, breathing CO_2 enriched air, or administering a dose of acetazolamide.[11] These maneuvers can be cumbersome. Further, prior methods of calculating CO_2 vasoreactivity used linear modeling and frequency-dependent linear Transfer Functions.[12-15] End-tidal CO2 fluctuates during normal breathing. However, the relation between end tidal CO_2 and BFV is nonlinear and there is low linear coherence at

low frequencies. [16] Hence, the linear methods may not be very representative of the physiology of CO_2 vasoreactivity during normal breathing. Deriving CO_2-vasoreactivity measure from these fluctuations requires signal modelling methods that address these limitations (non-linearity and low frequency).

In this study, we aimed at investigating the association between BFV autoregulation and CO_2 vasoreactivity with cognitive function in hypertension. We derived the CO_2 vasoreactivity using a novel modeling method developed by our coauthor from the resting respiratory fluctuations of end-tidal CO_2 as well as using conventional methods during breathing CO_2-enriched air and hyperventilation. We compared the two methods in their correlation with cognitive function.

Materials and Methods

Study description and participants

This is an analysis of the baseline data collected on the participants of a randomized clinical trial. The study design of the original clinical trial was described elsewhere.[17] Briefly, this was a 12-month double-blind randomized controlled clinical trial of candesartan, lisinopril, or HCTZ. The data used in this analysis was collected at baseline. Inclusion criteria were: 60 years or older; hypertension (systolic blood pressure (SBP) of 140 mm Hg or greater or diastolic blood pressure (DBP) 90 mm Hg or greater or receiving antihypertensive medications); and executive dysfunction based on a score less than 10 on the executive clock draw test (CLOX1).[18] To exclude those with possible dementia we did not enroll those with a Mini-Mental-State-Exam (MMSE)<20 or those with a clinical diagnosis of Alzheimer's disease or other dementias. Exclusion criteria included: intolerance to the study medications; SBP >200 or DBP >110 mm Hg; elevated serum creatinine (>2.0 mg/dl) or serum potassium (5.3 meq/dl) at baseline; receiving more than two antihypertensive medications; congestive heart failure, diabetes mellitus; stroke; and inability to perform the study procedures or unwilling to stop currently used antihypertensive medications. Subjects were recruited from the greater Boston area.

Participants who were receiving antihypertensive medications were instructed to stop their current therapy. All participants were provided with a portable automated blood pressure monitor and study personnel trained each participant on the use of the blood pressure monitor. All participants received written instructions on tapering and discontinuation of antihypertensive medications and description of symptoms associated with possible adverse events. They were asked to measure blood pressure two times a day (morning and before sleep) and record them into a diary. Contact by the study personnel was twice weekly for review of blood pressures. The timeline for medication was a decrease by 25% to 50% during week 1, 50% to 75% during week 2, and 100% for week 3. Baseline measurements were performed after 3 weeks. Subjects with significant blood pressure elevations (SBP >180/100 mm Hg) for at least two consecutive times or who developed hypertension-related symptoms were excluded (failed taper), asked to resume their usual dose of antihypertensive medications, and were referred back to their primary care physician for chronic blood pressure management as usual. The Institutional Review Board of the Hebrew SeniorLife

approved the study and all participants provided written informed consent. The study was also registered in ClinicalTrials.gov (NCT00605072).

Baseline measurements were made (when the patients were off antihypertensive medications). Neuropsychological assessments included the Trail Making Test (TMT) parts A, B. [19] TMT is a benchmark test for executive function. We also calculated TMT part B minus part A (B-A) which adjusts the TMT for the motor speed and dexterity of the participant.[20] We also used revised Hopkins Verbal Learning Test (HVLT), and the Digit Span Test (DST). The HVLT assesses both immediate and delayed recall and recognition abilities. The DST measures attention.

Cerebral Hemodynamic measurements

BFV was measured in the middle cerebral artery using Transcranial Doppler (TCD) ultrasonography (2-MHz probe placed over the temporal bone, MultiDop X4, DWL-Transcranial Doppler Systems Inc., Sterling, VA). Heart rate and blood pressure were simultaneously measured using continuous ECG recording and a Finometer™ (FMS, Finapress Measurement Systems, Arnhem, Netherlands). End-tidal CO_2 was measured using a CO_2 analyzer (VacuMed, Ventura, CA) attached to a nasal cannula. Measurements were obtained under the following conditions: (1) at rest while sitting for 5 minutes with normal breathing room-air; (2) during standing for 1 minute; (3) during breathing 8% CO_2 air for 2 minutes; and (4) during hyperventilating for 2 minutes. Beat-to-beat values of BFV, blood pressure and end-tidal CO_2 were computed off-line from these continuous measurements using the recorded R-R intervals of the ECG.

Calculation of cerebral hemodynamics indices

The obtained beat-to-beat time-series data were analysed offline using Matlab (Mathworks, Natik, MA). We used the data that were measured after being off all antihypertensive medications.

Autoregulation—Using the data obtained at rest and during the one minute stand, we calculated an index of autoregulation as the change in cerebrovascular resistance (CVR) denoted as delta-CVR. CVR is calculated as ratio of mean arterial pressure divided by BFV.

CO_2 vasoreactivity—This was calculated as the rate or slope of the change in BFV vs end-tidal CO_2 during breathing enriched CO_2 and hyperventilation: $^{\Delta BFV}/_{\Delta Petco_2}$, where $Petco_2$ ranges from hypocapnia to hypercapnia.

Principal Dynamic Modes—We also used the method of Principal Dynamic Modes (PDM) to calculate CO_2 vasoreactivity from 5-minute normal breathing data.[21,22] PDM constitute an efficient basis of reference functions for the representation of the system's kernels that can describe the dynamic relationship between input variables (e.g. blood pressure and end-tidal CO_2) and output variables (e.g. BFV) in a reliable and compact manner. A diagrammatic representation of the PDM modelling approach is shown in Figure 1. Using the PDM-based models that have predictive capability, we can compute appropriate “physiomarkers” of cerebral autoregulation and vasoreactivity for each subject by

simulating the resulting BFV changes for given changes of blood pressure and CO_2, respectively, during normal breathing. These physiomarkers were computed as the time-average of the PDM-based model-predicted responses (beat-to-beat BFV) to step changes of end-tidal CO_2 for vasoreactivity or arterial blood pressure for cerebral autoregulation relative to the respective baseline value over 30 seconds. The magnitude of the step change was set equal to one standard deviation of the actual CO_2 or pressure data recorded in each subject (i.e. adjusted to the observed operating range of each subject) and was centered around the baseline CO_2 or pressure value (i.e. the average of the respective recorded data). This magnitude varied between 2.4 mmHg and 4.7 mmHg for the pressure changes, and between 1.6 mmHg and 5.9 mmHg for the CO_2 changes in this set of patients. In order to obtain credible PDM-based model estimates we need at least 3 min of reliable beat-to-beat dat.[23] We extracted the 3-minute data from the 5-minute data recorded at rest. Since CO_2 may increase blood pressure, these model-based indices were computed under closed-loop conditions where such reciprocal effects (i.e. of blood flow and CO_2 changes upon blood pressure) are also taken into account.[24] A full mathematical description of this method was described elsewhere.[25] The PDM-based models are not ad hoc models, but rather they are canonical representations of cerebral hemodynamics, yielding indices of physiological meaning. Specifically, the resulting PDM-based CO_2 vasoreactivity index represents the time-average of BFV increase over 30 sec per unit of imposed of %change in end-tidal CO_2 (cm/sec/%mmHg). Likewise, the resulting model-based cerebral autoregulation index represents the time-average of cerebral flow velocity increase (in the middle cerebral artery) over 30 sec per unit of imposed arterial pressure change (cm/sec/mmHg).

Statistical analysis

Associations of the “traditional” and PDM-derived physiomarkers of cerebral hemodynamics with cognitive function were assessed using linear regression models: the cognitive score as the dependent variable and the physiomarkers as the independent variable. Trail Making Test (TMT) score distributions were skewed and hence we use natural logarithmic transformations. All regression models were adjusted for age and systolic blood pressure. To assess the degree of association between PDM-derived indices or the “traditional” linear physiomarkers with cognitive function we calculated two measures: the Pearson correlation and the Partial R^2 (as a measure of the proportion of the explained variation in the cognitive test score by the physiomarkers) calculated form the multiple regression models.[26] The SAS statistical (Carey, NC) package was used for these analyses.

Results

Of the 63 eligible participants, 53 tapered their antihypertensive medications and were assessed at baseline. Of those 47(89%) had successful insonation of the middle cerebral artery. PDM-based indices were obtainable from 41 subjects because 6 had temporary displacement of the nasal cannula that reduced the available continuous time-series data-record to less than 3 min, which renders the indices inaccurate.

Basic clinical and hemodynamic characteristics are provided in Table 1. There was a weak but significant correlation between the CO_2 vasoreactivity measures using the two methods of calculations: R^2 for the correlation was 14%, p=0.02. This correlation was stronger during the hypoventilation phase of the hyper/hypoventilation protocol (R^2 was 21% for hypoventilation and 1% for hyperventilation).

After adjusting for age and systolic blood pressure, lower CO_2 vasoreactivity calculated as the rate (slope) of the change in BFV vs the change in end-tidal CO_2 during the hypo/hyperventilation procedure was associated with worse performance on executive function testing [TMT part B (p=0.009) and B-A (p=0.02)] but not the other cognitive domains as described in Table 2. Also, lower PDM-based index of CO_2 reactivity was associated with worse performances on TMT Part B (p=0.05) and TMT Part B-A (p=0.009).

Measures of association strength between executive function and CO_2 vasoreactivity were higher for the PDM-derived index of CO_2 vasoreactivity compared to the traditional measure: The Pearson correlation of TMT part B with the linear measure of CO_2 reactivity was 0.26 and with the PDM-derived index was 0.32. The partial R^2 was 0.07 for the traditional measure and 0.10 for the PDM-derived index. For TMT part B-A, the Pearson correlations were 0.22 for the traditional measure and 0.41 for the PDM-derived index. The partial R^2 was 0.05 for the traditional vs 0.17 for the PDM-derived index. Illustrative scatter-plots with a fitted regression line of TMT Part B-A data versus the CO_2-reactivity indices are shown in Figure 2.

Sitting BFV values and autoregulation (delta-CVR or PDM derived) were not related to executive function as shown in Table 3. There was no association between any cerebral hemodynamic measure and the scores on the HVLT or the forward and backward DST.

Discussion

Our main findings are: lower CO_2 vasoreactivity may be associated with worse executive function in hypertensive older adults and calculating CO_2 vasoreactivity using non-linear modelling technique from resting measurements of BFV and end-tidal CO_2 normal breathing fluctuations is at least as useful as using the protocol of hypercapnia to hypocapnia. Our preliminary data suggest that the measure calculated using the normal breathing data might even be a stronger marker for executive function deficit in hypertension.

Although the underlying mechanisms are unknown, hypertension may preferentially affect executive function even in the absence of memory deficits. Prior studies have shown that hypertension is associated with a decline in CO_2 vasoreactivity.[8] This study extends this association to show that the lower the CO_2 vasoreactivity the worse the executive function performance. This suggests that damage to the microvasculature function may explain the observed predilection of atrophy in the prefrontal lobe and executive dysfunction with hypertension.[28] CO_2 vasoreactivity may be a marker of endothelial-dependent dilatation and the ability to react to changes in PH in the arterioles.[29,30] Wide use of CO_2 vasoreactivity has been limited by the need to induce wide alterations in end-tidal CO_2 (e.g.

hyperventilation or breath-holding). In this study we provide reliable quantitative means to assess CO_2 vasoreactivity using only resting-state data of BFV, end-tidal CO_2, and systemic blood pressure. The advanced mathematical modelling using PDMs can be automated to provide rapid, on-line physiomarkers of potential clinical utility (e.g. the vasoreactivity and autoregulation indices proposed herein) while the patient is being clinically assessed or shortly after. The present study provides a first step to making this approach clinically feasible.

Multiple prior mathematical models of cerebral blood flow regulation have been developed. [31] The PDM model-based indices in this study performed as good as or even better than the traditional CO_2 vasoreactivity measures in explaining the variance in executive function performance. The relative ease of obtaining these measures, compared to a full hypercapnia/hypocapnia protocol, and their association with executive function, in contrast to memory or attention, provide further impetus to explore these measures in future research.

Hypertension is associated with decreased CO_2 vasoreactivity and antihypertensive therapy has a significant effect on cerebral blood flow and hence our study may be more reflective of the underlying pathological changes that occur with hypertension. The relative small sample size is a limitation of this study. Another limitation is the lack of neuroimaging to confirm presence of microvascular disease, and the lack of measurement of intracranial pressure, which is an important factor in determining BFV. Despite these limitations, our data add critical information to the field that in hypertension lower CO_2 vasoreactivity may be associated with lower executive function but not memory declines. It is a first and critical step in unravelling the complex relation between hypertension and cognition.

Conclusion

Our study suggests that lower CO_2 vasoreactivity is associated with worse executive function. PDM-based modeling using BFV and end-tidal CO_2 during normal breathing would decrease time and inconvenience of measuring this important vascular marker. Future research is needed on the utility of this measure in hypertensive brain health and related clinical trials.

Acknowledgments

Sources of Funding: Dr. Hajjar and the AVEC trial are supported by grant 1 K23 AG030057 from the National Institute on Aging. This work was supported in part by the Biomedical Simulations Resource at the University of Southern California under NIH/NIBIB grant P41-EB001978.

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Abbreviations

BFV	Blood flow velocity
CO_2	Carbon Dioxide
Delta-CVR	change in cerebrovascular resistance from sit to stand
DST	Digit span test
HVLT	Hopkins verbal learning test
PDM	Principal Dynamic Modes
TCD	Transcranial Doppler
TMT	Trail Making Test

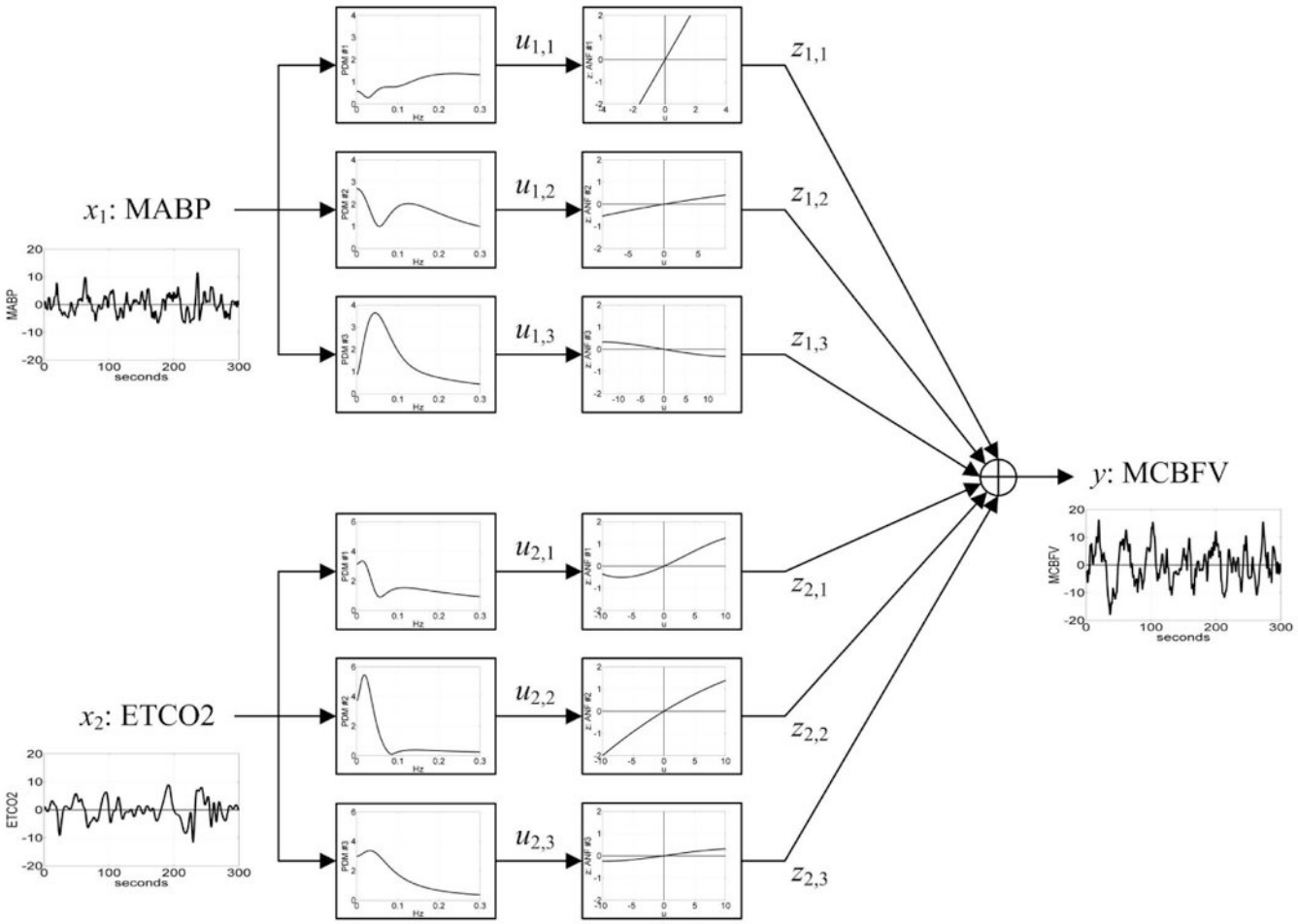

Figure 1.

Block-diagram of PDM-based model of the cerebral hemodynamics with output y(t) the beat-to-beat Mean Cerebral Flow Velocity (MCBFV) and two inputs: $x_1(t)$ the Mean Arterial Blood Pressure (MABP) and $x_2(t)$ the End-Tidal CO2 (ETCO2). There are three PDMs for each of the two inputs shown in the diagram in the frequency domain (Transfer Functions) which are common for all subjects and are estimated from the data. The output $u_{j,m(t)}$ of the j^{th} PDM for the m^{th} input is the convolution of the PDM with the respective input (linear filter operation). The Associated Nonlinear Function (ANF) following each PDM is a cubic polynomial representing the system nonlinearities for the respective PDM and it is estimated from the data of each subject (subjectspecific). The output y(t) is the sum of all ANF outputs $[z_{j,m}]$ and a constant offset value c_0.

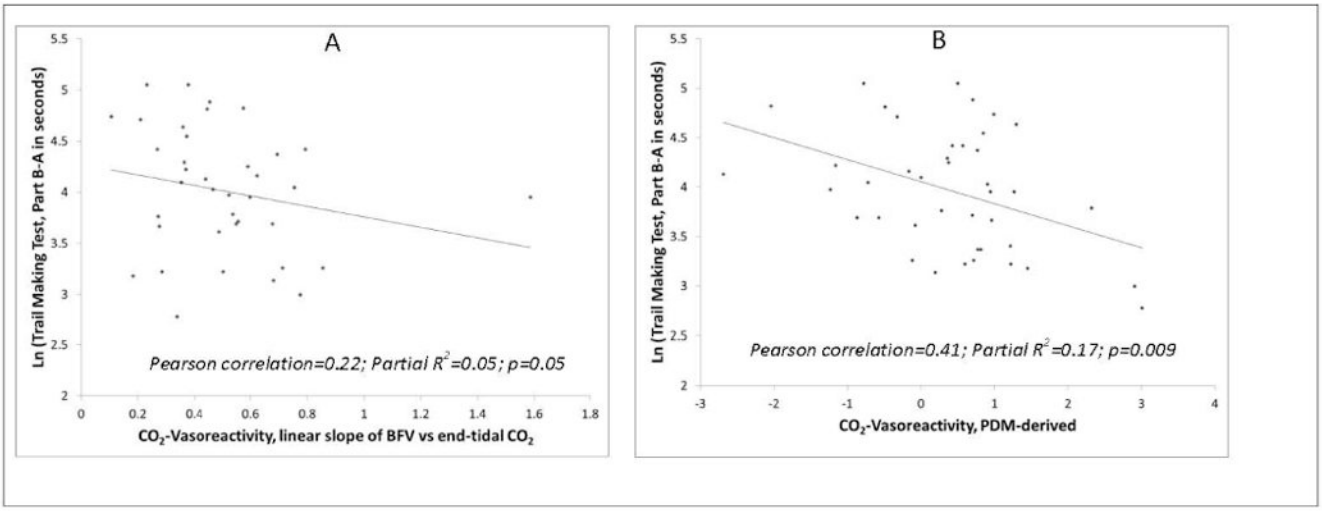

Figure 2.

Scatter-plot and regression association between Trail Making Test, Part B-A included as the natural logarithm of Trail Making Test score (**A**) linear measure of CO_2 vasoreactivity (cm/sec/mm Hg end-tidal CO_2) and (**B**) PDM-derived measure of CO_2 vasoreactivity (in cm/sec/%CO_2 change). Partial R^2 and p-values were obtained from the multiple regression models adjusting for age and mean systolic blood pressure.

Table 1

Socio-demographic, clinical, neuropsychiatric, and cerebral hemodynamic characteristics of the final sample available for this analysis

Measure	Mean (Standard deviation) or number (frequency)
N	41
Age, years	71 (7)
Women, %	25 (61%)
African American, %	10 (24%)
White, %	29 (70%)
High school education or lower,%	8 (20%)
College education or higher, %	33 (80%)
Body Mass Index, Kg/m^2	28.78 (6.09)
Baseline cognitive function	
Mini Mental State Examination	26 (2)
Executive Clock Draw test	8 (2)
Blood pressure and Heart Rate Sitting	
Systolic Blood Pressure, mm Hg	151 (16)
Diastolic Blood pressure, mm Hg	83 (9)
Heart rate, beats per min	65 (9)
Cognitive function	
Trail Making Test-Part A, seconds	37 (12)
Trail Making Test-Part B, seconds	100 (45)
Trail Making Test-Part B-A, seconds	63 (38)
Hopkins Verbal Learning Test, Recall	8 (3)
Hopkins Verbal Learning Test, Recognition	23 (2)
Digit Span, Forward	6 (1)
Digit Span, Backward	4 (2)
Cerebral Hemodynamics	
Sitting Blood Flow Velocity, cm/sec	28.34 (6.54)
CO_2-reactivity (slope of Blood Flow Velocity vsend-tidal CO_2)	0.51 (0.26)
CVR change (sit to stand)	-0.45 (0.52)
Principal Dynamic Modes indices	
Pressure Regulation Index	-0.13 (0.80)
CO_2 Vasoreactivity index	0.41 (1.10)

Table 2

Association between cognitive function and resting blood flow velocity, conventional CO_2 vasoreactivity and autoregulation indices

	Resting BFV	CO_2 vasoreactivity	CVR change (sit-to-stand)
	β (SE), p-value	β (SE), p-value	β (SE), p-value
TMT, Part A	0.001(0.01), p=0.69	-0.4(0.2), p=0.03	0.2(0.1), p=0.05
TMT, Part B	-0.01(0.01), p=0.31	-0.7(0.3), p=0.009	-0.02(0.14), p=0.91
TMT, Part B-A	-0.02(0.02), p=0.34	-0.9(0.4), p=0.02	-0.13(0.21), p=0.53
HVLT, Recall	0.11(0.07), p=0.13	0.4(1.8), p=0.83	0.95(0.9), p=0.3
HVLT, recognition	0.003(0.05), p=0.95	0.07(1.1), p=0.95	0.21(0.59), p=0.73
Digit Span, Forward	-0.05(0.04), p=0.19	-0.5(0.9), p=0.56	-0.19(0.47), p=0.69
Digit Span, Backwards	0.2(0.22), p=0.38	0.5(1), p=0.61	0.3(0.54), p=0.59

BFV: Blood flow velocity; CVR : Cerebrovascular resistance; SE= standard error; TMT=Trail Making Test; B-A: Part B minus Part A; HVLT: Hopkins Verbal Learning Test. Slope (β), standard errors and p-values were obtained from the regression models adjusted for age and systolic blood pressure. TMT (A, B, and B-A) were transformed using a logarithmic transformation due to their skewed distribution.

Table 3

Association between cognitive function and PDM derived indices of cerebrovascular reactivity and pressure autoregulation

	CO2 Vasoreactivity	Pressure Autoregulation
	β (SE), p-value	β (SE), p-value
TMT, Part A	0.02(0.04), p=0.63	0.09(0.06), p=0.15
TMT, Part B	-0.11(0.06), p=0.05	0.04(0.08), p=0.68
TMT, Part B-A	-0.22(0.08), p=0.01	0.01(0.13), p=0.95
HVLT, Recall	0.4(0.38), p=0.3	0.04(0.54), p=0.94
HVLT, recognition	0.35(0.24), p=0.16	-0.22(0.35), p=0.53
Digit Span, Forward	-0.16(0.2), p=0.42	-0.42(0.27), p=0.13
Digit Span, Backwards	0.2(0.22), p=0.38	-0.16(0.32), p=0.63

SE= standard error; TMT=Trail Making Test; B-A: Part B minus Part A; HVLT: Hopkins Verbal Learning Test; Slope (β), standard errors and p-values were obtained from the regression models adjusted for age and systolic blood pressure. TMT (A, B, and B-A) were transformed using a logarithmic transformation due to their skewed distribution.