Assessment of Cerebrovascular Reactivity during Resting State Breathing and Its Correlation with Cognitive Function in Hypertension

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Key Words

Hypertension · Cerebral blood flow · Trail-Making Test

Abstract

Background: Hypertension is associated with cognitive deficits, particularly executive function, and decreased cerebral microvascular responsiveness to CO₂ (CO₂ vasoreactivity). The relation between CO₂ vasoreactivity and executive function is not known. Protocols to assess CO₂ vasoreactivity are cumbersome and require inhaling a CO₂-enriched gas. We explored the ability to measure CO₂ vasoreactivity using end-tidal CO₂ 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 and normally breathing for 5 min, followed by breathing 5% CO₂ gas and hyperventilation for 2 min each. We calculated CO₂ vasoreactivity as the rate of BFV change from hypoventilation to hyperventilation, and as a model-derived measure using the normal breathing data. The latter was derived using non-linear principal dynamic modes (PDM), which modelled the dynamic effect of fluctuations in end-tidal CO₂ and blood pressure upon BFV during normal room-air respiration. Multiple regression analyses were used to correlate cerebral hemodynamics with cognitive measures. **Results:** Data were

collected from 41 individuals with hypertension (mean age 71 years, 24% African Americans, 61% women, off antihypertensive therapy). Lower CO₂ vasoreactivity was associated with a worse executive function test score using both calculation methods: p value using the hyper/hypoventilation data was 0.04 and from the PDM analysis was 0.009. PDM calculations showed a stronger correlation with executive function (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 CO₂ vasoreactivity ($R^2 = 14\%$, $p = 0.02$). **Conclusion:** This study suggests that the decrease in CO₂ vasoreactivity in hypertension is associated with lower executive function. This may offer new insight into the vascular underpinning of cognitive decline in hypertension. We demonstrate that calculating CO₂ vasoreactivity is possible during normal breathing. If replicated in future studies, this may offer a more convenient clinical way to assess CO₂ vasoreactivity in hypertension and cognitive disorders.

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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 microvas-

culature of the brain. Hypertension is also associated with decreased responsiveness to CO₂ [4], which may be an early marker of microvascular dysfunction and impaired endothelial health [5]. We therefore hypothesized that lower CO₂ 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 CO₂ (CO₂ vasoreactivity). Hypertension and aging are associated with decreased CO₂ vasoreactivity but relatively preserved autoregulation [6–8]. Lower CO₂ 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 CO₂ can be induced by breath holding, breathing CO₂-enriched air, or administering a dose of acetazolamide [11]. These maneuvers can be cumbersome. Furthermore, prior methods of calculating CO₂ 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 CO₂ 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 CO₂ vasoreactivity during normal breathing. Deriving CO₂ vasoreactivity measure from these fluctuations requires signal modelling methods that address these limitations (nonlinearity and low frequency).

In this study, we aimed at investigating the association between BFV autoregulation and CO₂ vasoreactivity with cognitive function in hypertension. We derived the CO₂ vasoreactivity using a novel modeling method developed by our coauthor from the resting respiratory fluctuations of end-tidal CO₂, as well as using conventional methods during breathing CO₂-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 were collected at baseline. Inclusion criteria were: 60 years or older; hypertension (systolic blood pressure, SBP, 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-Drawing Test (CLOX1) [18]. To exclude those with possible dementia we did not enroll those with a Mini-Mental State Examination <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. The 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 its use. All participants received written instructions on the tapering and discontinuation of antihypertensive medications and description of symptoms associated with possible adverse events. They were asked to measure blood pressure twice a day (morning and before sleep) and record them into a diary. Contact by the study personnel was twice weekly for the review of blood pressures. The timeline for medication was a decrease by 25–50% during week 1, 50–75% 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 measurements or who developed hypertension-related symptoms were excluded (failed taper), were 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 with 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 the revised Hopkins Verbal Learning Test (HVLT), and the Digit Span Test (DST). The HVLT assesses both immediate and delayed recall and recognition abilities, whilst the DST measures attention.

Cerebral Hemodynamic Measurements

BFV was measured in the middle cerebral artery using transcranial Doppler ultrasonography (2-MHz probe placed over the temporal bone; MultiDop X4, DWL-Transcranial Doppler Systems Inc., Sterling, Va., USA). Heart rate and blood pressure were simultaneously measured using a continuous ECG recording and a Finometer™ (FMS, Finapres Measurement Systems, Arnhem, The Netherlands). End-tidal CO₂ was measured using a CO₂ analyzer (VacuMed, Ventura, Calif., USA) attached to a nasal cannula. Measurements were obtained under the following conditions: (1) at rest while sitting for 5 min with normal breathing of

Fig. 1. Block diagram of the PDM-based model of cerebral hemodynamics with the output $y(t)$ being the beat-to-beat mean cerebral BFV (MCBFV) and two inputs: $x_1(t)$ the mean arterial blood pressure (MABP) and $x_2(t)$ the end-tidal CO_2 (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 (subject specific). The output $y(t)$ is the sum of all ANF outputs ($z_{j,m}$) and a constant offset value c_0 .

room air; (2) during standing for 1 min; (3) during breathing 8% CO_2 air for 2 min, and (4) during hyperventilating for 2 min. Beat-to-beat values of BFV, blood pressure and end-tidal CO_2 were computed offline 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 analyzed offline using Matlab (Mathworks, Natick, Mass., USA). We used the data that were measured after being off all antihypertensive medications.

Autoregulation

Using the data obtained at rest and during the 1-min stand, we calculated an index of autoregulation as the change in cerebrovascular resistance (CVR) denoted as delta-CVR. CVR is calculated as the ratio of mean arterial pressure divided by BFV.

CO_2 Vasoreactivity

This was calculated as the rate or slope of the change in BFV versus end-tidal CO_2 during breathing enriched CO_2 and hyperventilation, with 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-min 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 simu-

lating the resulting BFV changes for given changes of blood pressure and CO₂, 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 CO₂ for vasoreactivity or arterial blood pressure for cerebral autoregulation relative to the respective baseline value over 30 s. The magnitude of the step change was set equal to one standard deviation of the actual CO₂ or pressure data recorded in each subject (i.e. adjusted to the observed operating range of each subject) and was centered around the baseline CO₂ or pressure value (i.e. the average of the respective recorded data). This magnitude varied between 2.4 and 4.7 mm Hg for the pressure changes, and between 1.6 and 5.9 mm Hg for the CO₂ 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 data [23]. We extracted the 3-min data from the 5-min data recorded at rest. Since CO₂ may increase blood pressure, these model-based indices were computed under closed-loop conditions where such reciprocal effects (i.e. of blood flow and CO₂ 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 CO₂ vasoreactivity index represents the time average of BFV increase over 30 s per unit of imposed percent change in end-tidal CO₂ (cm/s/% mm Hg). Likewise, the resulting model-based cerebral autoregulation index represents the time-average of cerebral flow velocity increase (in the middle cerebral artery) over 30 s per unit of imposed arterial pressure change (cm/s/mm Hg).

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. TMT score distributions were skewed and hence we used natural logarithmic transformations. All regression models were adjusted for age and SBP. 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 R² (as a measure of the proportion of the explained variation in the cognitive test score by the physiomarkers) calculated from the multiple regression models [26]. The SAS statistical package (SAS, Carey, N.C., USA) 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.

Table 1. Socio-demographic, clinical, neuropsychiatric and cerebral hemodynamic characteristics of the final sample available for this analysis

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)
<i>Baseline cognitive function</i>	
Mini-Mental State Examination	26 (2)
CLOX1	8 (2)
<i>Blood pressure and heart rate when sitting</i>	
SBP, mm Hg	151 (16)
DBP, mm Hg	83 (9)
Heart rate, beats/min	65 (9)
<i>Cognitive function</i>	
TMT part A, s	37 (12)
TMT part B, s	100 (45)
TMT part B-A, s	63 (38)
HVLT recall	8 (3)
HVLT recognition	23 (2)
DST forward	6 (1)
DST backward	4 (2)
<i>Cerebral hemodynamics</i>	
Sitting blood flow velocity, cm/s	28.34 (6.54)
CO ₂ reactivity (slope of blood flow velocity versus end-tidal CO ₂)	0.51 (0.26)
CVR change (sit-to-stand)	-0.45 (0.52)
<i>Principal dynamic modes indices</i>	
Pressure regulation index	-0.13 (0.80)
CO ₂ vasoreactivity index	0.41 (1.10)

Data for each measure are either mean with standard deviation in parentheses, or number with frequency in parentheses.

Basic clinical and hemodynamic characteristics are provided in table 1. There was a weak but significant correlation between the CO₂ vasoreactivity measures using the two calculation methods: R² for the correlation was 14%, p = 0.02. This correlation was stronger during the hypoventilation phase of the hyper/hypoventilation protocol (R² was 21% for hypoventilation and 1% for hypoventilation).

After adjusting for age and SBP, lower CO₂ vasoreactivity, calculated as the rate (slope) of change in BFV versus the change in end-tidal CO₂ 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, a lower PDM-based index of

Table 2. Association between cognitive function and resting BFV, conventional CO₂ vasoreactivity and autoregulation indices

	Resting BFV		CO ₂ vasoreactivity		CVR change (sit-to-stand)	
	β	p	β	p	β	p
TMT part A	0.001 (0.01)	0.69	-0.4 (0.2)	0.03	0.2 (0.1)	0.05
TMT part B	-0.01 (0.01)	0.31	-0.7 (0.3)	0.009	-0.02 (0.14)	0.91
TMT part B-A	-0.02 (0.02)	0.34	-0.9 (0.4)	0.02	-0.13 (0.21)	0.53
HVLT recall	0.11 (0.07)	0.13	0.4 (1.8)	0.83	0.95 (0.9)	0.3
HVLT recognition	0.003 (0.05)	0.95	0.07 (1.1)	0.95	0.21 (0.59)	0.73
DST forward	-0.05 (0.04)	0.19	-0.5 (0.9)	0.56	-0.19 (0.47)	0.69
DST backwards	0.2 (0.22)	0.38	0.5 (1)	0.61	0.3 (0.54)	0.59

Values in parentheses are standard error. Slope (β), standard errors and p values were obtained from the regression models adjusted for age and SBP. TMT (A, B and B-A) were transformed using a logarithmic transformation due to their skewed distribution.

Fig. 2. Scatter-plot and regression association between TMT part B-A included as the natural logarithm of TMT score and linear measure of CO₂ vasoreactivity (cm/s/mm Hg end-tidal CO₂; **a**)

and PDM-derived measure of CO₂ vasoreactivity (in cm/s/%CO₂ change; **b**). Partial R² and p values were obtained from the multiple regression models adjusting for age and mean SBP.

CO₂ 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 CO₂ vasoreactivity were higher for the PDM-derived index of CO₂ vasoreactivity compared to the traditional measure: the Pearson correlation of TMT part B with the linear measure of CO₂ reactivity was 0.26 and with the PDM-derived index was 0.32. The partial R² 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 R² was 0.05 for the traditional versus 0.17 for the PDM-derived index. Illustrative scatter-plots with a fitted regression line of

TMT part B-A data versus the CO₂-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 that lower CO₂ vasoreactivity may be associated with worse executive function in hypertensive older adults, and calculating CO₂ vasoreactiv-

Table 3. Association between cognitive function and PDM-derived indices of cerebrovascular reactivity and pressure autoregulation

	CO ₂ vasoreactivity		Pressure autoregulation	
	β	P	β	P
TMT part A	0.02 (0.04)	0.63	0.09 (0.06)	0.15
TMT part B	-0.11 (0.06)	0.05	0.04 (0.08)	0.68
TMT part B-A	-0.22 (0.08)	0.01	0.01 (0.13)	0.95
HVLT recall	0.4 (0.38)	0.3	0.04 (0.54)	0.94
HVLT recognition	0.35 (0.24)	0.16	-0.22 (0.35)	0.53
DST forward	-0.16 (0.2)	0.42	-0.42 (0.27)	0.13
DST backwards	0.2 (0.22)	0.38	-0.16 (0.32)	0.63

Values in parentheses are standard error. Slope (β), standard errors and p values were obtained from the regression models adjusted for age and SBP. TMT (A, B and B-A) were transformed using a logarithmic transformation due to their skewed distribution.

ity using a nonlinear modelling technique from resting measurements of BFV and end-tidal CO₂ 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 CO₂ vasoreactivity [8]. This study extends this association to show that the lower the CO₂ vasoreactivity, the worse the executive function performance is. This suggests that damage to the microvasculature function may explain the observed predilection of atrophy in the prefrontal lobe and executive dysfunction with hypertension [27]. CO₂ vasoreactivity may be a marker of endothelial-dependent dilatation and the ability to react to changes in pH in the arterioles [28, 29]. Wide use of CO₂ vasoreactivity has been limited by the need to induce wide alterations in end-tidal CO₂ (e.g. hyperventilation or breath holding). In this study we provide reliable quantitative means to assess CO₂ vasoreactivity using only resting-state data of BFV, end-tidal CO₂ and systemic blood pressure. The advanced mathematical modelling using PDM can be automated to provide rapid, online physiometers 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 [30]. The PDM model-based indices in this study performed as well as or even better than the traditional CO₂ 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 CO₂ 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 relatively small sample size is a limitation of this study. Another limitation is the lack of neuroimaging to confirm the 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 CO₂ 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 CO₂ vasoreactivity is associated with worse executive function. PDM-based modeling using BFV and end-tidal CO₂ during normal breathing would decrease the 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.

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Disclosure Statement

None.

References

- Novak V, Hajjar I: The relationship between blood pressure and cognitive function. *Nat Rev Cardiol* 2010;7:686–698.
- Vicario A, Martinez CD, Baretto D, Diaz Casale A, Nicolosi L: Hypertension and cognitive decline: impact on executive function. *J Clin Hypertens* (Greenwich) 2005;7:598–604.
- Liu-Ambrose T, Pang MY, Eng JJ: Executive function is independently associated with performances of balance and mobility in community-dwelling older adults after mild stroke: implications for falls prevention. *Cerebrovasc Dis* 2007;23:203–210.
- Hajjar I, Zhao P, Alsop D, Novak V: Hypertension and cerebral vasoreactivity: a continuous arterial spin labeling magnetic resonance imaging study. *Hypertension* 2010;56:859–864.
- Cohen RA: Hypertension and cerebral blood flow: implications for the development of vascular cognitive impairment in the elderly. *Stroke* 2007;38:1715–1717.
- Carey BJ, Eames PJ, Blake MJ, Panerai RB, Potter JF: Dynamic cerebral autoregulation is unaffected by aging. *Stroke* 2000;31:2895–2900.
- Eames PJ, Blake MJ, Panerai RB, Potter JF: Cerebral autoregulation indices are unimpaired by hypertension in middle aged and older people. *Am J Hypertens* 2003;16:746–753.
- Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V: Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke* 2000;31:1897–1903.
- Portegies ML, de Bruijn RF, Hofman A, Koudstaal PJ, Ikram MA: Cerebral vasomotor reactivity and risk of mortality: the Rotterdam study. *Stroke* 2014;45:42–47.
- Yonas H, Smith HA, Durham SR, Penhney SL, Johnson DW: Increased stroke risk predicted by compromised cerebral blood flow reactivity. *J Neurosurg* 1993;79:483–489.
- Totaro R, Marini C, Baldassarre M, Carolei A: Cerebrovascular reactivity evaluated by transcranial Doppler: reproducibility of different methods. *Cerebrovasc Dis* 1999;9:142–145.
- Aoi M, Gremaud P, Tran HT, Novak V, Olufsen MS: Modeling cerebral blood flow and regulation. *Conf Proc IEEE Eng Med Biol Soc* 2009;2009:5470–5473.
- Peterson EC, Wang Z, Britz G: Regulation of cerebral blood flow. *Int J Vasc Med* 2011;2011:523–525.
- Giller CA: The frequency-dependent behavior of cerebral autoregulation. *Neurosurgery* 1990;27:362–368.
- Zhang R, Zuckerman JH, Giller CA, Levine BD: Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol* 1998;274:H233–H241.
- Mitsis GD, Ainslie PN, Poulin MJ, Robbins PA, Marmarelis VZ: Nonlinear modeling of the dynamic effects of arterial pressure and blood gas variations on cerebral blood flow in healthy humans. *Adv Exp Med Biol* 2004;551:259–265.
- Hajjar I, Hart M, Milberg W, Novak V, Lipsitz L: The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: role of the renin angiotensin system inhibition. *BMC Geriatr* 2009;9:48.
- Royall DR, Cordes JA, Polk M: CLOX: an executive clock drawing task. *J Neurol Neurosurg Psychiatry* 1998;64:588–594.
- Gordon NG: The trail making test in neuropsychological diagnosis. *J Clin Psychol* 1972;28:167–169.
- Corrigan JD, Hinkeldey NS: Relationships between parts A and B of the Trail Making Test. *J Clin Psychol* 1987;43:402–409.
- Marmarelis VZ, Shin DC, Orme ME, Zhang R: Model-based quantification of cerebral hemodynamics as a physiomarker for Alzheimer's disease? *Ann Biomed Eng* 2013;41:2296–2317.
- Marmarelis VZ, Shin DC, Orme ME, Zhang R: Closed-loop dynamic modeling of cerebral hemodynamics. *Ann Biomed Eng* 2013;41:1029–1048.
- Mitsis GD, Poulin MJ, Robbins PA, Marmarelis VZ: Nonlinear modeling of the dynamic effects of arterial pressure and CO₂ variations on cerebral blood flow in healthy humans. *IEEE Trans Biomed Eng* 2004;51:1932–1943.
- Garnham J, Panerai RB, Naylor AR, Evans DH: Cerebrovascular response to dynamic changes in pCO₂. *Cerebrovasc Dis* 1999;9:146–151.
- Marmarelis VZ, Shin DC, Orme ME, Zhang R: Closed-loop dynamic modeling of cerebral hemodynamics. *Ann Biomed Eng* 2013;41:1029–1048.
- Guilford JP, Fruchter B: *Fundamental Statistics in Psychology and Education*, ed 6. New York, McGraw-Hill, 1978.
- Raz N, Rodrigue KM, Acker JD: Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behav Neurosci* 2003;117:1169–1180.
- Heistad DD, Mayhan WG, Coyle P, Baumbach GL: Impaired dilatation of cerebral arterioles in chronic hypertension. *Blood Vessels* 1990;27:258–262.
- Mayhan WG, Faraci FM, Heistad DD: Impairment of endothelium-dependent responses of cerebral arterioles in chronic hypertension. *Am J Physiol* 1987;253:H1435–H1440.
- Gao E, Young WL, Pile-Spellman J, Ornstein E, Ma Q: Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. *Am J Physiol* 1998;274:H1023–H1031.