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RESEARCH ARTICLE

The effects of body mass index on cerebral blood flow velocity

Magdy Selim
Richard Jones
Peter Novak
Peng Zhao
Vera Novak

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M. Selim, MD, PhD
Dept. of Neurology, Stroke Division
Beth Israel Deaconess Medical Center
Boston (MA), USA

R. Jones, ScD
Hebrew Senior Life
Institute for Aging Research
Boston (MA), USA

P. Novak, MD, PhD
Dept. of Neurology
University of Massachusetts
Worcester (MA), USA

P. Zhao, PhD · V. Novak, MD, PhD (✉)
Division of Gerontology
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston (MA) 02215, USA
Tel.: +1-617/632-8680
Fax: +1-617/632-8675
E-Mail: vnovak@bidmc.harvard.edu

Abstract *Objective* Obesity is a risk factor for cerebrovascular disease. We aimed to determine the effects of high body mass index (BMI) on cerebral blood flow regulation in patients with type-2 diabetes mellitus, hypertension, and stroke. *Methods* We analyzed data from 90 controls, 30 diabetics, 45 hypertensives, and 32 ischemic stroke patients who underwent transcranial Doppler for evaluation of blood flow velocities (BFV) in the middle cerebral arteries (MCA) and cerebrovascular resistance (CVR) during supine rest and head-up tilt. This study was a cross-sectional analysis. We used a structural equation multiple indicators modeling to determine the effects of BMI and other background variables (age, sex, race, smoking, alcohol use, and systolic blood pressure) on cerebral BFV. *Results* Higher BMI ($P = 0.02$) and age ($P = 0.004$) were associated with lower mean BFV during baseline, independent of diagnosis of diabetes mellitus, hypertension or stroke, and after adjusting for all background variables and vessel diameters. Men, especially those with stroke, had a lower mean BFV than women ($P = 0.01$). CVR increased with BMI ($P = 0.001$) at baseline and during head-up tilt ($P = 0.02$), and was elevated in obese subjects ($P = 0.004$) compared to normal weight subjects across all groups. *Interpretation* High BMI is associated with a reduction in cerebral BFV and increased CVR. These findings indicate that obesity can adversely affect cerebral blood flow and resistance in the cerebrovascular bed, independent of diagnosis of type-2 diabetes, hypertension or stroke. Obesity may contribute to cerebromicrovascular disease, and affect clinical functional outcomes of the older population.

Key words body mass index · obesity · cerebral blood flow · transcranial Doppler · stroke · diabetes · cerebrovascular resistance · tilt

Introduction

Patients with diabetes, hypertension, and previous history of stroke have increased risk for cerebrovascular diseases, stroke, and cognitive decline [18, 25, 31]. Body mass index (BMI) is increasingly recognized as a risk factor for stroke, cardiovascular disease, and cognitive decline, in addition to known factors such as age, hypertension, smoking, and alcohol use [8, 10]. Diabetes mellitus, hypertension and cardiovascular risk factors exert complex effects on cerebral microvasculature [4, 14] which accelerate cerebral blood flow (CBF) decline that occurs with

normal aging. Little is known about the impact of patients' characteristics, including BMI, on cerebral hemodynamics in these conditions. Transcranial Doppler (TCD) ultrasound is used as a surrogate for non-invasive assessment of CBF [21] by measuring blood flow velocities in major arteries of the brain at baseline and during orthostatic stress [26]. Therefore, we aimed to determine the impact of BMI and background clinical characteristics on blood flow velocities (BFV) in middle cerebral arteries and cerebrovascular resistance in patients with diabetes, hypertension, and stroke in comparison with controls at baseline and during head-up tilt.

Materials and methods

Subjects

Initial recruitment began in the autonomic nervous system laboratory at the department of neurology at The Ohio State University. Recruitment during the latter part of the study was carried through the syncope and falls in the elderly (SAFE) laboratory at the Beth Israel Deaconess medical center in Boston under the direction of the same investigators (VN, PN) and using identical protocols and methodology. All subjects provided a written informed consent to an IRB approved protocol. Participants were prospectively recruited according to the following inclusion/exclusion criteria: Age ≥50 to ≤85 years. Control group—subjects who were normotensive, had normal hemoglobin A1c (HbA1c) level, had no history of stroke or transient ischemic attacks (TIA), and were not treated for any systemic disease except hypercholesterolemia. Diabetes group—patients diagnosed with type-2 diabetes mellitus (average 12.8 ± 11.5 years), and had no history of stroke or TIA. Hypertension group—subjects treated for essential hypertension, who had no history of stroke or TIA, and had normal HbA1c. Stroke group—included subjects with history of ischemic stroke, who had a documented infarct on MRI or CT scan affecting <1/3 of MCA territory with a modified Rankin scale score <4.

Fifty-three percent of patients in the stroke group had a left-sided infarct; 47% had a right-sided infarct. Forty-one percent of strokes were attributed to large artery disease; 25% to small vessel (lacunar) disease; and 10% to cardioembolism. Stroke mechanism was undetermined in the remaining 24% of patients. Approximately 7% of participants in the diabetes group were also hypertensives, while 19% of stroke patients were also treated for hypertension, and 3% were diabetics. Subjects with a history of stroke (except for the stroke group), clinically significant cardiac disease, arrhythmias, significant nephropathy, kidney or liver transplant, renal or congestive heart failure, uncontrolled hypertension, known carotid artery stenosis >50%, neurological or other systemic disorders, and hemorrhagic stroke were not eligible to participate in this study.

Eligibility and risk factors assessment

We screened potential subjects with detailed medical history and physical and neurological examinations, electrocardiogram, and routine laboratory tests that included serum glucose and renal function, HbA1C, lipid panel (including triglycerides, and total, LDL and HDL cholesterol), complete blood cell and differential count, and urine analysis. We calculated the atherogenic index in the plasma as log (triglycerides/HDL-cholesterol, mmol/l) [9]. We measured the subjects' weight and height, and calculated the BMI in kilograms per square meter.

TCD examinations

All TCD examinations were conducted early in the morning, at least 2 hours after the last meal, and performed by the same sonographer (VN) using MultiDop ×4 TCD machine (Neuroscan Inc., El Paso, TX, USA). Antihypertensive medications were tapered over a 1-week period and withdrawn on the day of the examination. Anticholinergics and other cardioactive medications were held before the study on the same day. Hypoglycemic agents, anticoagulants and other medications were allowed. The subjects rested in a supine position for 10 minutes and then the table was titled upright to 70° for 10 minutes. The right (MCAR) and left (MCAL) MCA were insonated from the temporal windows with 2-MHz pulsed Doppler probes. Each probe was positioned to record the maximal flow velocities and stabilized using a 3-dimensional head frame positioning system. Peak-systolic, end-diastolic, and mean BFV were measured for each MCA. Systolic (SBP) and diastolic (DBP) blood pressures during the examination were recorded beat-to-beat from a finger with a Finapres device (Ohmeda Monitoring Systems, Englewood, CO, USA) and intermittently with BP measurement tonography [23]. Beat-to-beat BP recordings were averaged over the resting period (5–10 minutes). Cerebrovascular resistance was calculated as mean BP divided by mean BFV in MCAR and MCAL and as a Gosling's pulsatility index (systolic-diastolic BFV/mean BFV) [1].

Magnetic resonance imaging

A subset of 79 patients underwent imaging studies at the magnetic resonance imaging center at the Beth Israel Deaconess medical center at the GE 3 Tesla VHI scanner using a quadrature head coil. Anatomical images of intracranial vasculature were obtained using 3D-MR angiography (time of flight, TOF) with the following parameters: TE/TR = 3.9/38 ms, flip angle of 25°, 2 mm slice thickness, −1 mm skip, 20 cm × 20 cm FOV, 384 × 224 matrix size, pixel size 0.39 × 0.39 mm and tissue imaging included T1-weighted inversion-recovery prepared fast gradient echo (IR-FGE), 3D magnetization prepared rapid gradient echo (MP-RAGE) and fluid-attenuated inversion recovery (FLAIR) sequences. The MCA and internal carotid arteries (ICA) radii were measured by the software "Medical Image Processing, Analysis, and Visualization" (MIPAV), Biomedical Imaging Research Services Section, NIH, USA. The scale for an image can be defined to achieve accurate measurements with resolution up to one pixel size (0.39 mm × 0.39 mm). For each vessel, the diameter was measured at three locations and averaged.

Statistical analysis

We conducted two types of analyses. In the first set of analyses we used a structural equation modeling procedure called multiple groups, multiple indicators, and multiple cause (MIMIC) modeling to explore the relationship between diabetes, hypertension and stroke, and clinical and behavioral characteristics related to CBF [12]. MIMIC model details are provided in the Appendix. This model does not aim to predict absolute CBF values. The MIMIC model uses CBF as a latent variable that cannot be directly measured but it is represented by two indicators, in our case mean BFV in right and left MCAs. The model predicts the

effects of multiple covariates (age, sex, race, BMI, SBP, smoking and alcohol use); and test for differences in the prediction across clinical group while allowing for heteroskedasticity in CBF across study population. MIMIC model parameters were interpreted as ANCOVA-type regression parameters. Overall model fit was evaluated by using chi-square statistic, where degrees of freedom are tied to the number of parameter estimates in the means and covariance matrix (high P values implying good fit). We also used the root mean square error of approximation (RMSEA) and the comparative fit index, where RMSEA provides a measure of discrepancy per model degree of freedom [6]. The RMSEA approaches 0 as model fit improves. We accepted values close to 0.06 or less that represent adequately fitting models [5], and comparative fit index values greater than 0.95 that are generally accepted as describing adequately fitting models. In the second set of analyses we used the MANOVA and the least square models to evaluate the effects of BMI on CVR at baseline and during tilt, atherogenic index, Gosling's pulsatility index, MCA and ICA diameters, and other laboratory variables. Models were adjusted for age, sex and group. Statistical significance was set as $P \leq 0.05$.

Results

A total of 212 subjects were enrolled into the study. Of these, 15 subjects were excluded because of poor quality TCD examinations, poor temporal windows, or missing elements of the dataset. Data from the remaining 197 subjects (90 healthy controls, 30 diabetics, 45 hypertensives, and 32 stroke patients) were included in the analysis. MRI analysis is based on data from 79 (40 controls, 22 diabetics, 10 hypertensives, and 7 stroke patients). Table 1 summarizes the characteristics of each of these four groups including demographics, risk factors, laboratory values, pulsatility index, intracranial vessels diameters, and medications. Demographic factors and hematological parameters including lipids were similar among the groups, except, as expected, for systolic blood pres-

Table 1 Characteristics of the study population

	Controls	Diabetes	Hypertension	Stroke
Number	90	30	45	32
Men/women	42/48	17/13	18/27	13/17
Age (years)	56.8 ± 13.2	61.3 ± 7.2	52.9 ± 11.3	58.2 + 9.8
African–American (%)	6	10	35	15
BMI (kg/m^2)	26.1 ± 4.8	28 ± 4.9	30.9 ± 8.5	30.5 ± 8.1
Smoking history (%)	36	43	18	44
Current alcohol use (%)	60	47	58	50
Glucose (mg/dl)	85.0 ± 16.3	105.8 ± 48.5	86.7 ± 10.2	83.9 ± 9.2
Total cholesterol (mg/dl)	176.9 ± 16.6	170.3 ± 18.2	178.2 ± 25.8	169.9 ± 15.3
Triglycerides (mg/dl)	103.5 ± 31.2	112.2 ± 71.3	122.5 ± 19.1	100.5 ± 24.3
HDL cholesterol (mg/dl)	63.5 ± 15.0	57.3 ± 18.3	67.1 ± 22.6	56.7 ± 13.3
LDL cholesterol calc (mg/dl)	101.4 ± 19.3	96.5 ± 46.0	91.1 ± 23.0	87.4 ± 11.3
Atherogenic index plasma	0.43 ± 0.48	0.50 ± 0.69	0.54 ± 0.15	0.36 ± 0.53
Hematocrit (%)	40.9 ± 2.7	41.9 ± 2.8	40.6 ± 3.6	41.4 ± 3.8
R MCA (mm)	2.52 ± 0.36	2.7 ± 0.29	2.49 ± 0.23	2.52 ± 0.33
L MCA (mm)	2.59 ± 0.36	2.63 ± 0.35	2.35 ± 0.19	2.56 ± 0.31
R ICA (mm)	5.28 ± 0.55	5.11 ± 0.62	5.44 ± 0.57	5.1 ± 0.33
L ICA (mm)	5.3 ± 0.46	5.26 ± 0.64	5.56 ± 0.48	5.31 ± 0.44
Frequency of medications use				
Antithrombotics				
APL (%)	20	33	27	62
OAC (%)	0	0	2	19
Lipid-lowering agents				
Statins (%)	11	47	20	44
Others (%)	4	3	0	3
Hypoglycemic agents				
Insulin (%)	0	37	0	0
Oral hypoglycemics (%)	0	50	2	3
Antihypertensives				
ACE inhibitors (%)	0	27	47	25
ARBs (%)	0	13	7	13
Beta blockers (%)	6	17	9	19
Calcium antagonists (%)	0	7	20	16
Diuretics (%)	0	7	36	16
Others				
Estrogen (%)	8	7	27	16
Antiparkinsonians (%)	0	3	0	0

APL, antiplatelets; OAC, oral anticoagulation; ARBs, angiotensin receptor blockers; R MCA, right middle cerebral artery; L MCA, left middle cerebral artery; R ICA, right internal carotid artery; LICA, left internal carotid artery

sure ($P = 0.008$) and glucose ($P = 0.02$). History of smoking, and alcohol consumption was not different. MCA and ICA diameters for both sides were not different among the groups. There were no significant differences among subjects in the diabetes, hypertension and stroke groups who were treated with angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, β-blockers, statins, or antithrombotics. We found no significant interaction between antithrombotics, ACE inhibitors, or statins and BFVs.

Cerebral blood flow velocities and vascular resistance

We modeled the effects of patient characteristics on baseline CBF (as a latent variable) by using mean BFV in both MCAs. Diabetics had a lower mean baseline BFV compared to controls ($P = 0.017$), but mean BFV was similar among the other groups. This effect was no longer significant after adjusting for background variables.

Table 2 summarizes the results of the final fitted MIMIC model. This model estimated the effects of background variables (age, BMI, SBP, smoking and current alcohol use) within each group and across the whole population. The model reveals that older age ($P = 0.004$) and higher body mass index ($P = 0.022$) are associated with lower mean BFV in all 4 groups; SBP is positively related to mean BFV among hypertensive subjects ($P = 0.007$); and that men relative to women in the stroke group have lower mean BFV ($P = 0.01$). In the control group, age ($P = 0.004$) and BMI ($P = 0.022$) were associated with lower BFV. No significant relationship was found for smoking and alcohol use. Higher BMI remained associated with lower BFV after adjusting background variables and vessel diameters ($P = 0.017$). Figure 1a shows a plot of BMI, and age-adjusted mean MCAR and MCAL BFV, and Figure 1b shows that mean BFV in MCAR ($P = 0.017$) and MCAL ($P = 0.0002$) were higher for normal weight (BMI < 25 kg/m^2) than overweight (BMI 25–30 kg/m^2) and obese subjects (BMI > 30 kg/m^2) in all study groups.

Table 2 Standardized regression parameters of MIMIC models of BFV on subject background characteristics

Standardized regression coefficients	Controls	Diabetes	Hypertension	Stroke
Age	**−0.26***	−0.14	−0.20	**−0.18***
Male sex	−0.13	−0.13	−0.12	**−0.98***
African-American	−0.34	−0.34	−0.31	−0.31
BMI	**−0.15***	**−0.15***	**−0.24***	**−0.24***
SBP	−0.12	−0.16	**0.40***	−0.11
Ever smoked	−0.15	−0.15	−0.14	−0.14
Current alcohol use	0.28	0.29	0.26	0.26

Table entries are standardized regression coefficients and describe the per standard deviation (SD) increase in BFV per SD increase in the predictor for continuous predictors (age, BMI, SBP) and the SD difference in BFV for subjects with the characteristic for the binary predictors (male sex, African–American race, smoking history, and current alcohol use)
Boldface indicates significant group differences in the effect of the predictor relative to other groups, * $P < 0.05$

Table 3 summarizes the hemodynamic characteristics of each of the four groups during baseline and head-up tilt. Controls had significantly lower CVR in MCAR and MCAL at baseline and during head-up tilt. After adjusting for age, sex and group, BMI was independently associated with increased vascular resistance (CVR MCAR $P = 0.03$, CVR MCAL $P = 0.0002$) during baseline and head-up tilt (CVR MCAR $P = 0.02$, CVR MCAL $P = 0.04$). Gosling's pulsatility index was used as a second measure of vascular resistance and was also associated with a higher BMI at baseline (MCAR BMI < 25 0.71 ± 0.17; BMI 25–30 0.80 ± 0.2, BMI > 30 0.71 ± 0.19, $P = 0.037$) and MCAL (BMI < 25 0.71 ± 0.13; BMI 25–30 0.80 ± 0.12, BMI > 30 0.71 ± 0.15, $P = 0.01$).

Figure 1c shows that baseline CVR increases with BMI for normal weight, overweight, and obese subjects (CVR MCAR $= P = 0.008$, CVR MCAL $P = 0.002$) in all groups, and was elevated in obese subjects ($P = 0.004$) compared to normal weight subjects across all groups. Figure 1d shows that CVR during head-up tilt (corrected for hydrostatic pressure change) also increased with BMI (CVR MCAR $= P = 0.009$, CVR MCAL $P = 0.001$).

MCA diameter

MCA diameters were not significantly different between the groups and among normal weight, overweight and obese subjects. MCA diameters were not significantly associated with BMI (right MCA $P = 0.39$, left MCA $P = 0.16$). BFVs in MCA s were not significantly associated with MCA diameters (MCAR $r^2 = 0.025$, $P = 0.20$; MCAL $r^2 = 0.034$, $P = 0.1$). Higher BMI remained associated with lower BFV after adjusting background variables and vessel diameters ($P = 0.017$).

Atherogenic index, lipids, hematocrit

Atherogenic index was not different among the groups, but was lower in women compared to men (0.26 ± 0.41 vs. 0.64 ± 0.53 mmol/l, $P = 0.004$). Expectedly, the atherogenic index was positively associated with BMI ($P = 0.0006$, $r = 0.39$) and male sex ($P = 0.02$; $r = 0.39$). Higher BMI ($P = 0.01$) and male sex ($P < 0.0001$, $r = 0.57$) were associated with

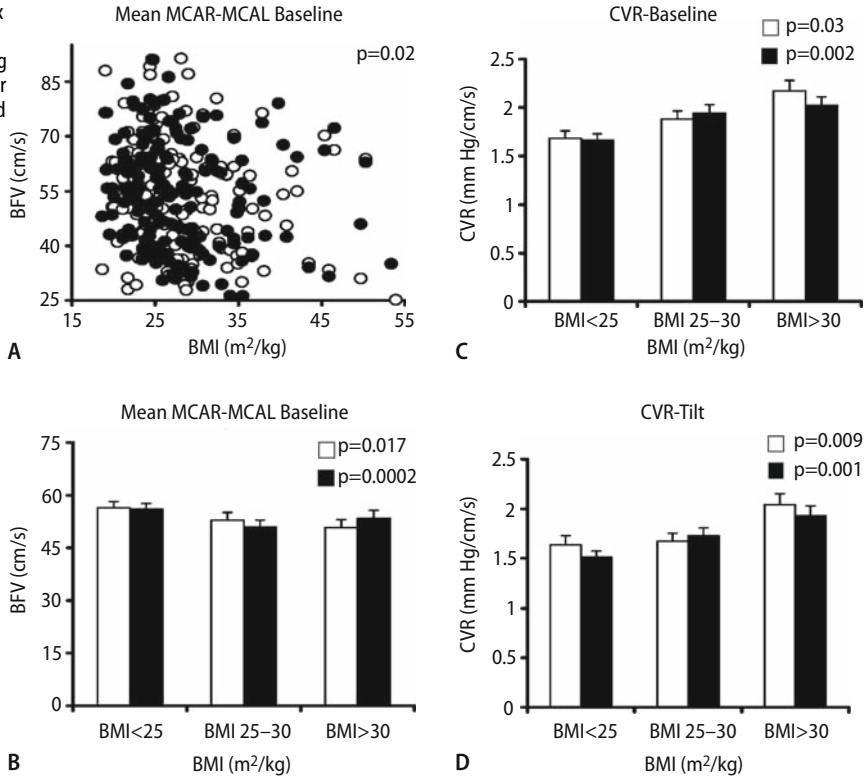

Fig. 1 **A**, **B** The relationship between body mass index (*BMI*) and age-adjusted mean blood flow velocities in right and left middle cerebral artery (MCAR, MCAL) during baseline in all groups. **C**, **D** The average cerebrovascular resistance (CVR in MCAR and MCAL during baseline and head-up tilt (mean ± SE)

lower HDL levels, and higher LDL levels ($P = 0.04$, $r = 0.37$) and triglycerides ($P = 0.0075$, $r = 0.45$). Women in our study had lower hemoglobin and hematocrit (39.3 ± 2.8 vs. 43.0 ± 2.3%), and athrogenic index (0.26 ± 0.43 vs. 0.64 ± 0.54 mmol/l, $P = 0.004$ than men, and lower hematocrit was associated with

Table 3 Hemodynamic parameters during baseline and head up tilt

	Controls	Diabetes	Hypertension	Stroke	Groups&side
BFV MCAR (cm/s)	54.4 ± 15.1	46.3 ± 16.5	60 ± 15.4	52.2 ± 17	0.19
BFV MCAL (cm/s)	55.6 ± 13.7	49.9 ± 15.7	55.9 ± 16.5	51.2 ± 22	
Heart rate (bpm)	64.8 ± 8.3***	69.8 ± 17.4	70.5 ± 9.6	73.1 ± 12.4	0.0008
SBP (mm Hg)	121 ± 14***	130 ± 19	148 ± 14	135 ± 14	<0.0001
DBP (mm Hg)	65.96 ± 10.1***	64.9 ± 10*	82.4 ± 16.9	73.7 ± 14.2	<0.0001
CVR MCAR (mm Hg/cm per second)	1.7 ± 0.6**	2.2 ± 0.9	1.9 ± 0.6	2.1 ± 0.9	0.0034
CVR MCAL (mm Hg/cm per second)	1.6 ± 0.4***	1.9 ± 0.6	2.0 ± 0.7	2.2 ± 0.9	
PI MCAR (cm/s)	0.7 ± 0.1*	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.0005
PI MCAL (cm/s)	0.7 ± 0.1**	0.7 ± 0.1	0.8 ± 0.2	0.9 ± 0.3	
Baseline $EtCO_2$ (mm Hg)	37.3 ± 7.7	34.9 ± 5.6	36.6 ± 6.5	35.9 ± 3.8	0.33
TILT					
BFV MCAR (cm/s)	48.4 ± 14.0	44.7 ± 14.0	55.6 ± 18.1	50.1 ± 17.9	0.41
BFV MCAL (cm/s)	49.5 ± 12.0	46.9 ± 12.8	52.5 ± 16.9	49.3 ± 21.6	
HR (bpm)	77.4 ± 10.8	80.0 ± 12.7	75.2 ± 12.2	80.9 ± 12.9	0.02
SBP (mm Hg)	122 ± 17.0***	131 ± 15.3	156 ± 14.0	142 ± 16.7	<0.0001
DBP (mm Hg)	73.2 ± 11.0***	73.5 ± 12.1	89.2 ± 19.4	83.4 ± 18.7	<0.0001
CVR MCAR (mm Hg/cm per second)	1.6 ± 0.6**	1.9 ± 0.8	1.8 ± 0.0.7	1.9 ± 0.9	0.0096
CVR MCAL (mm Hg/cm per second)	1.5 ± 0.4***	1.7 ± 0.0.7	1.9 ± 0.0.7	1.8 ± 0.7	
PI MCAR (cm/s)	0.7 ± 0.2	0.7 ± 0.3	0.8 ± 0.2	0.9 ± 0.6	0.01
PI MCAL (cm/s)	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	
Baseline $EtCO_2$	32.1 ± 4.3	32.4 ± 4.3	34.0 ± 4.5	33.3 ± 3.3	0.1

Values are expressed as percentages or mean ± SD, model was adjusted for age and sex, MANOVA used for paired variables
indicates values that were significantly different in control group compared to other groups * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$
CVR tilt was adjusted for position

higher BFV ($r = 0.42$, $P = 0.01$). Hematocrit was not different in people with higher BMI. There was relative heterogeneity of stroke group in terms of stroke etiology. Stroke side, etiology and type of antihypertensive medications, however were not significant factors in our analyses.

Discussion

Our results show that cerebral flow velocities decrease with increasing body mass and age in all groups, and that the male sex is associated with lower BFV especially among stroke patients. Higher BMI is also associated with increased CVR during supine rest and orthostatic stress. The effects of BMI on BFV and CVR are independent of those for age and sex and vessel diameter. These findings indicate that obesity may adversely affect flow velocity and resistance in the cerebrovascular bed, independent of the diagnosis of type-2 diabetes, hypertension, or stroke.

Our findings that increased BMI, regardless of age or sex, is associated with reduced cerebral BFV and increased CVR are novel and intriguing. Body mass has been recently recognized as a risk factor for cerebrovascular disease and cognitive decline in addition to age and other cardiovascular factors [8, 10]. Obesity is associated with increased intima-media thickness that may affect pulsatility large arteries, and might be the consequence of metabolic dysregulation, associated dyslipidemia, inflammation, or other mechanisms [11, 24]. In multivariate analysis, excess body weight and male sex were linked to progressive arterial dysfunction and impaired both endothelium mediated and independent vasodilatation [3, 13] with subsequent decrease in arterial blood flow [7]. In addition, obesity is also associated with abnormalities in microvascular patterns, reduced small vessel density, inflammation and impaired endothelial function and vascular reactivity [28, 29] in peripheral and possibly even in central vascular beds.

Our observation of increased CVR suggests that obesity may also affect the cerebral microvasculature and vasoreactivity during orthostatic stress. Few studies have reported on the relationship between BMI and blood flow regulation and have found positive relationship between obesity and arterial stiffness [32], reduced large and small vessel arterial compliance [2], and reduced distensibility including carotid arteries. Simillarly, in our study, we found greater resistance in the larger intracerebral arteries in obese and overweight subjects. Cerebral blood flow during head-up tilt is maintained by vasodilatation and decreased resistance of arterioles that compensate for reduced systolic blood pressure and intracranial pressure [20]. Our findings of higher CVR in obese subjects support the notion that obesity also affects vasoreactivity of cerebral microvasculature during orthostatic stress. We did not find a relationship between BMI and the diameter of MCAs on 3D MR-angiography in a subset of 79 patients in this population, thus reputing the notion that reduced BFV would be due to an increased MCA diameter.

Obesity, as manifested by increased BMI, emerged as the only modifiable characteristic associated with decreased cerebral BFV in our study. This can have important therapeutic implications. Meyer et al. [17] reported increased carotid intima-media thickness (IMT), impaired endothelial function, and flow-mediated vasodilatation in 76 young obese subjects, and showed that regular exercise for 6 months restored endothelial function, decreased IMT by 6%, and increased FMD by 127%, suggesting that the effects of obesity on blood vessels and flow can be reversed by exercise and weight reduction.

We found that men had lower BFV, especially among stroke patients, suggesting that changes in cerebral hemodynamics may be partly sex-dependent. Several pathophysiological, biochemical, and anatomical factors could potentially account for hemispheric differences in MCA BFV between sexes [16]. The observed gender differences in BFV in our study could be attributed to differences in blood rheology and atherogenic burden between the sexes. Women in our study had lower hematocrit, and athrogenic index than men, and lower hematocrit was associated with higher BFV. The preferential impact of sex on BFV in stroke patients needs further investigation because of a small sample size.

There are some factors that may limit the impact of this study. This analysis was cross-sectional and was focused on long-term relationship between BFV and background variables, rather than dynamics of autoregulation using beat-to-beat BFV-BP variablity or CO_2 reactivity, to assess long-term adaptation of cerebral vasculature at baseline and during orthostasis. Previous studies have shown that BFVs in the MCA correlate with invasive measurements of blood flow with xenon clearance [22], laser Doppler flux [15] and PET [30]. MCA diameter was not different between the groups and remains relatively constant under physiological conditions [27]. Further studies, however, are merited to assess complex effects of obesity on blood flow and tissue perfusion.

Conclusions

Our study provides evidence that obesity further affects cerebral blood flow velocities and vascular resistance in older adults in addition to already known effects of diabetes, hypertension, and stroke. These

findings may have important therapeutic implications. High BMI is a modifiable risk factor for stroke and cardiovascular disease, that can be linked to brain atrophy and cognitive decline [8, 10]. This warrants future prospective studies to assess whether the effects of high body mass on cerebral blood flow and vascular resistance can be reversed by weight reduction.

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Appendix

We used a structural equation modeling approach known as the MIMIC or multiple indicators, multiple cause model [5]. The MIMIC model is a structural equation modeling approach that characterizes the relationship between background exogenous variables (causes) and unobserved (latent) variables, which are indicated by imperfect representations of the underlying latent variable. In our case, the latent variable (CBF) was modeled as indicated by two observed variables, MCAR and MCAL BFVs. We did not aim to model absolute values of CBF. We used the measurement equation ($\mathbf{y} = \boldsymbol{\nu} + \boldsymbol{\Lambda}\eta + \varepsilon$), where η is 1×1 and contains the latent BFV variable; $\mathbf{y}$ contains MCAR and MCAL BFVs; $\boldsymbol{\nu}$ (vector) captures the intercepts in the measurement relations; $\boldsymbol{\Lambda}$ the loadings of the latent BFV variable in the observed variables; and ε the residuals in the measurement relations. To identify the model, we assumed that $\lambda_{11} = \lambda_{12} = 1$ and freely estimated the variance of the latent trait ($\mathrm{VAR}(\eta) = \boldsymbol{\Psi}$). The MIMIC model also includes a structural model, which relates the latent variable (η) to exogenous and so-called "causal" variables. This model can be represented with $\eta = \boldsymbol{\alpha} + \boldsymbol{\Gamma}\mathbf{x} + \boldsymbol{\zeta}$, where $\boldsymbol{\Gamma}$ contains regressions parameters expressing the increase in η per unit increase in the predictor variables in $\mathbf{x}$. Vector $\boldsymbol{\nu}$ contains the intercept of η, blood flow velocity, and $\boldsymbol{\zeta}$ residuals in the structural model. We considered the clinical group (controls, diabetics, hypertensives, or stroke patients) and participant's background variables (age, sex, and race), physiologic characteristics (BMI and SBP) and health behaviors (history of smoking, and current alcohol use) in $\mathbf{x}$. Associated regression parameters in $\boldsymbol{\Gamma}$ were interpreted as ANCOVA-type regression parameters when the background variables were discrete or linear regression parameters when the background variables were more or less continuously distributed, such as age, BMI, and SBP. We extended these MIMIC models to consider multiple groups, where clinical groups were used to separate participants and MIMIC models estimated simultaneously but separately within group. Initially we assumed the relationships of background variables and BFV were equal across group, but examined indices of model misspecification (model modification indices) and individually and iteratively relaxed equality constraints in $\boldsymbol{\Gamma}$ that would significantly improve model fit ($P < 0.05$). We evaluated the overall model fit by using chi-square statistic and associated P value, where degrees of freedom are tied to the number of parameter estimates and elements in the means and covariance matrix (high P values implying good fit). We also used the root mean square error of approximation (RMSEA) and the comparative fit index (CFI), where RMSEA provides a measure of discrepancy per model degree of freedom [6]. The RMSEA approaches 0 as model fit improves and values close to 0.06 or less represent adequately fitting models [5], and CFI values greater than 0.95 are generally accepted as describing adequately fitting models [19].

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