Different Relationship Between Systolic Blood Pressure and Cerebral Perfusion in Subjects With and Without Hypertension

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Abstract—Although there is an increasing agreement that hypertension is associated with cerebrovascular compromise, relationships between blood pressure (BP) and cerebral blood flow are not fully understood. It is not known what BP level, and consequently what therapeutic goal, is optimal for brain perfusion. Moreover, there is limited data on how BP affects hippocampal perfusion, a structure critically involved in memory. We conducted a cross-sectional (n=445) and longitudinal (n=185) study of adults and elderly without dementia or clinically apparent stroke, who underwent clinical examination and brain perfusion assessment (age 69.2±7.5 years, 62% women, 45% hypertensive). Linear models were used to test baseline BP-blood flow relationship and to examine how changes in BP influence changes in perfusion. In the entire group, systolic BP (SBP) was negatively related to cortical (β=−0.13, P=0.005) and hippocampal blood flow (β=-0.12, P=0.01). Notably, this negative relationship was apparent already in subjects without hypertension. Hypertensive subjects showed a quadratic relationship between SBP and hippocampal blood flow (β=−1.55, P=0.03): Perfusion was the highest in subjects with mid-range SBP around 125 mm Hg. Longitudinally, in hypertensive subjects perfusion increased with increased SBP at low baseline SBP but increased with decreased SBP at high baseline SBP. Cortical and hippocampal perfusion decrease with increasing SBP across the entire BP spectrum. However, in hypertension, there seems to be a window of mid-range SBP which maximizes perfusion. (*Hypertension*. 2019;73:197-205. DOI: 10.1161/HYPERTENSIONAHA.118.11233.) ● Online Data Supplement

Key Words: blood pressure ■ brain ■ hippocampus ■ hypertension ■ perfusion

Hypertension affects nearly 30% of the US population[1] and its prevalence increases with advancing age: over half of the population >60 years old is hypertensive.[2] The brain is among many organs damaged by high blood pressure (BP). Hypertension accelerates plaque formation in large vessels, leading to stroke.[3] It also causes vascular remodeling, lumen narrowing, and rarefaction of small vessels. These, in turn, result in decreased cerebral blood flow (CBF)[4,5] and impaired cerebral autoregulation[6,7] in hypertensive subjects compared with their normotensive peers. Despite our growing understanding of the relationship between BP and CBF there are important unanswered questions:

First, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure introduced the concept of prehypertension, defined as BP values 120 to 139/80 to 89 mm Hg.[2] Since then, ample data have confirmed that prehypertension infers a greater risk for cerebrovascular and cardiovascular morbidity than lower BP levels.[8] However, it is unknown if prehypertension is related to impaired CBF.

Second, there is limited data on the relationship between BP and CBF within the hypertensive group. Although high BP may cause progressive decrease in CBF because of structural changes in the vasculature, it seems that excessive lowering of BP may also lead to hypoperfusion, due to the shift of the autoregulatory curve to the right.[6,7] The exact functional relationship between BP and CBF is unknown, and it remains to be determined if an optimal BP value exists to maximize CBF.

Third, most studies have examined the relationship between BP and global cerebral perfusion. Much less is known about regional changes, in particular the impact of BP on hippocampal perfusion. The hippocampus plays a prominent role in cognition and it is one of the earliest brain structures affected during the progression of Alzheimer disease.[9] Given

that hypertension increases the risk of future cognitive decline,[10] including Alzheimer disease,[11] it would be of great value to examine the relationship between BP and hippocampal perfusion.

Accordingly, we undertook a large prospective study of cortical and hippocampal CBF in adults and elderly without dementia. Our key aim was to analyze and model both cross-sectional and longitudinal relationships between BP and brain perfusion.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects were recruited between January 2008 and November 2017 at the NYU School of Medicine, Center for Brain Health. They included volunteers responding to an advertisement, those interested in research participation and family members of cognitively impaired patients. All individuals signed the Institutional Review Board (ethical committee)-approved consent forms. Excluded were subjects with previous neocortical stroke, brain tumor, and life-long psychotic or depressive disorders.

From a pool of 489 subjects with perfusion data, we report here on 445 participants without dementia, >50 years old, with technically adequate arterial spin labeling (ASL) magnetic resonance imaging (MRI) and available clinical information (Figure S1 in the online-only Data Supplement presents exclusion criteria and participant flow). Dementia was excluded based on a physician-administered interview using the Brief Cognitive Rating Scale, rating on the Global Deterioration Scale,[12] and Clinical Dementia Rating.[13]

One hundred eighty-five individuals completed follow-up ASL exam and were subject to longitudinal CBF analyses. All subjects, but one, have been cognitively reassessed at follow-up. None of 184 individuals converted to dementia. Reasons for lack of follow-up are detailed in the online-only Data Supplement.

Clinical Assessment

All subjects underwent medical, psychiatric, and neurological assessments, blood tests, ECG, and MRI examinations. Blood samples taken in a fasting state were examined for complete blood count, liver function tests, metabolic, and lipid panel. BP was taken in a sitting position, after 5 minutes of rest. It was measured on the left upper arm using a manual sphygmomanometer.

Medication

The use of and the type of antihypertensive medications were recorded. The categories were angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, diuretics, and calcium channel blockers. For longitudinal analyses, we used an additional variable: change in antihypertensive medication—defined as increase, decrease, or no change in a number of medications over the interval. We also recorded the use of statins and glucose-lowering drugs.

Body mass index was calculated as weight/height^2 (kg)/(m)^2.

Global coronary heart disease risk was calculated based on the Framingham Heart Study equation. The heart disease was ascertained by medical interview. Details for both assessments are given in the online-only Data Supplement.

Study Groups

Hypertension was defined as current antihypertensive treatment or BP ≥140/90 mm Hg.[2] Two hundred subjects were classified as hypertensive. One hundred fifty-eight subjects were taking medication, and 42 were unmedicated with high BP recorded during their in-office visit.

Prehypertension was defined as BP of 120 to 139/80 to 89 mm Hg and no antihypertensive treatment.

Normotension was defined as BP: <120/80 mm Hg and no antihypertensive treatment.

Normotension and prehypertension subjects were analyzed together as a group without hypertension.

Magnetic Resonance Imaging

All MRI was performed on the 3T system (Siemens, Erlangen, Germany). Imaging protocol consisted of sagittal T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo, axial fluid attenuation inversion recovery, and perfusion ASL sequences. Details of MRI acquisition are given in the online-only Data Supplement.

Structural MRI Processing

Gray matter and intracranial volumes were estimated using Statistical Parametric Mapping segmentation procedure (SPM, version 8, with New-Segment extension).[14] Left and right hippocampal volumes were obtained with FreeSurfer version 6.0.[15] All volumes are presented as ratios to the intracranial volume.

The presence of white matter lesions (WMLs) was determined on fluid attenuation inversion recovery images. WMLs were graded from 0 to 3 on the Fazekas scale.[16] Periventricular WML and deep WML were graded separately.

CBF Sampling

Hippocampal, cortical, and WM region of interests (ROIs) were defined directly on high-resolution ASL images (to minimize partial volume errors; Figure 1; bottom right), using an in-house-developed software (https://wp.nyu.edu/firevoxel/). Cortical ROI encompassed temporal, parietal and in some cases also occipital cortex (Figure 1). For brevity, we will refer to this ROI as cortical as opposed to hippocampal. The process entailed (1) choosing a seed region in gray matter and WM, (2) constructing a WM ROI within 10% of the WM seed, restricted to the largest connected components and refined by automatic boundary erosion, (3) constructing gray matter ROI by intensity thresholding followed by automatic boundary erosion and removal of nonbrain tissue,[17] and (4) delineating right and left hippocampal regions. Each ROI was visually confirmed by investigators knowledgeable about the studied anatomy (L. Glodzik and H.J. Kim) who were blind to the subject's age and hypertension status. A batch process was then run to generate gray matter and hippocampal CBF. In the final step, all voxels with CBF >150 mL/(100 g min) were deemed to contain large blood vessels and were excluded from ROIs.[18]

Statistics

General

Categorical variables were compared with χ^2 tests. Student t test, ANOVA, or ANCOVA was used to compare group means for continuous variables. When appropriate, nonparametric U Mann-Whitney or Kruskal-Wallis ANOVA was used. All post hoc pair-wise comparisons were performed with Bonferroni correction. Correlations were checked using Pearson or Spearmen coefficient.

CBF data were acquired over the span of 9 years a 3T magnet that underwent significant hardware and software upgrades. Because the variability that corresponds to the 5 temporal epochs could contaminate our analyses, the perfusion values were Z scored separately by epoch, recentered and rescaled to eliminate this fixed bias. Please see in the online-only Data Supplement for more information about rescaling and its validation.

In all analyses, right and left hippocampal CBF and volume data were averaged.

Testing BP—CBF Relationship at Baseline

Relationships between continuous CBF (dependent variable) and BP were tested with separate stepwise (backward) linear regression. They were tested in the entire groups, as well as in subjects with and without hypertension separately. We first tested the relationship between CBF and individual variables: age, sex, periventricular WML, deep WML, global coronary heart disease score, heart disease, statin, and antihypertensive medication use. Variables significantly associated with CBF were included into regression models.

We hypothesized that in the hypertension group an optimal BP may exist, which maximizes perfusion. To test for the existence of the peak, the linear BP term was followed by entry of the quadratic
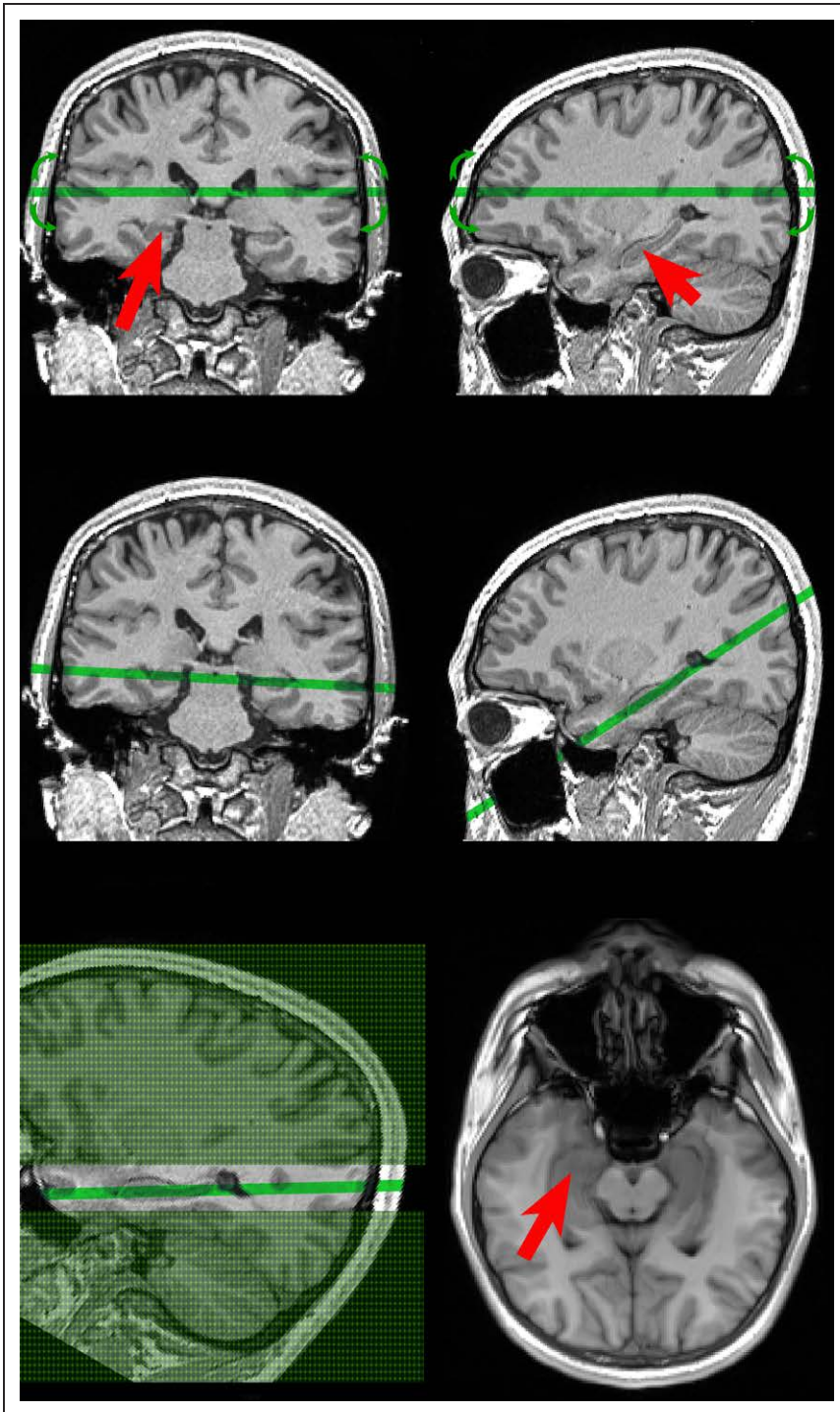
Figure 1. Selection of oblique hippocampal/ temporal cortex plane at the magnetic resonance imaging console. **Top**, A trained operator with experience in neuroanatomy is presented with coronal and sagittal views of 3-dimensional (3D) magnetization prepared rapid acquisition gradient echo volume. Red arrows indicate the **right** and the **left** hippocampus. The operator manipulates the position and the orientation of oblique acquisition plane while monitoring the 3D anatomic alignment (green line and green arrows). **Middle**, The arterial spin labeling exam begins after selecting the optimal plane through both the **left** and the **right** hippocampus. **Bottom left**, The green area represents tagging and the difference between slice nonselective (shaded in green) and slice-selective slab (not shaded). Note that slice-selective slab is 3.5× thicker than an imaged slice. **Bottom right**, The resulting balanced steady-state free precession image used to measure cerebral blood flow. Red arrows indicate the hippocampus.

term (BP²) in regression models examining the relationship to CBF. When a quadratic relationship $CBF = aBP^2 + bBP + c$ was confirmed (Figure 2D), the critical (maximum/minimum) BP value xc is given by the equation:

$$xc = -\frac{b}{2a} \qquad (1)$$

For linear regression, we report standardized beta values (β), as well unstandardized coefficient B with its 95% CI.

Testing BP—CBF Relationship Longitudinally
These relationships were tested using mixed model repeated measures. CBF was the dependent variable; continuous baseline BP, BP, and interaction between them were fixed terms; intercept was set as random. Subjects visits were set as repeated term. We also tested a model where BP was set as random. The model with the better fit (compared using likelihood ratio test) was chosen. Age, sex, medication use, change in a number of antihypertensive medications, and the presence of heart disease at baseline were tested and retained when significant.

To confirm the results we repeated our analyses using linear regression. For each subject, we created slopes for BP and CBF change over time. CBF slope was a dependent variable predicted by continuous baseline BP, BP slope, and interaction between them. The same covariates were tested in the models. Interaction terms were built with lower terms centered on their means. Collinearity was examined by assessing variance inflation factors.
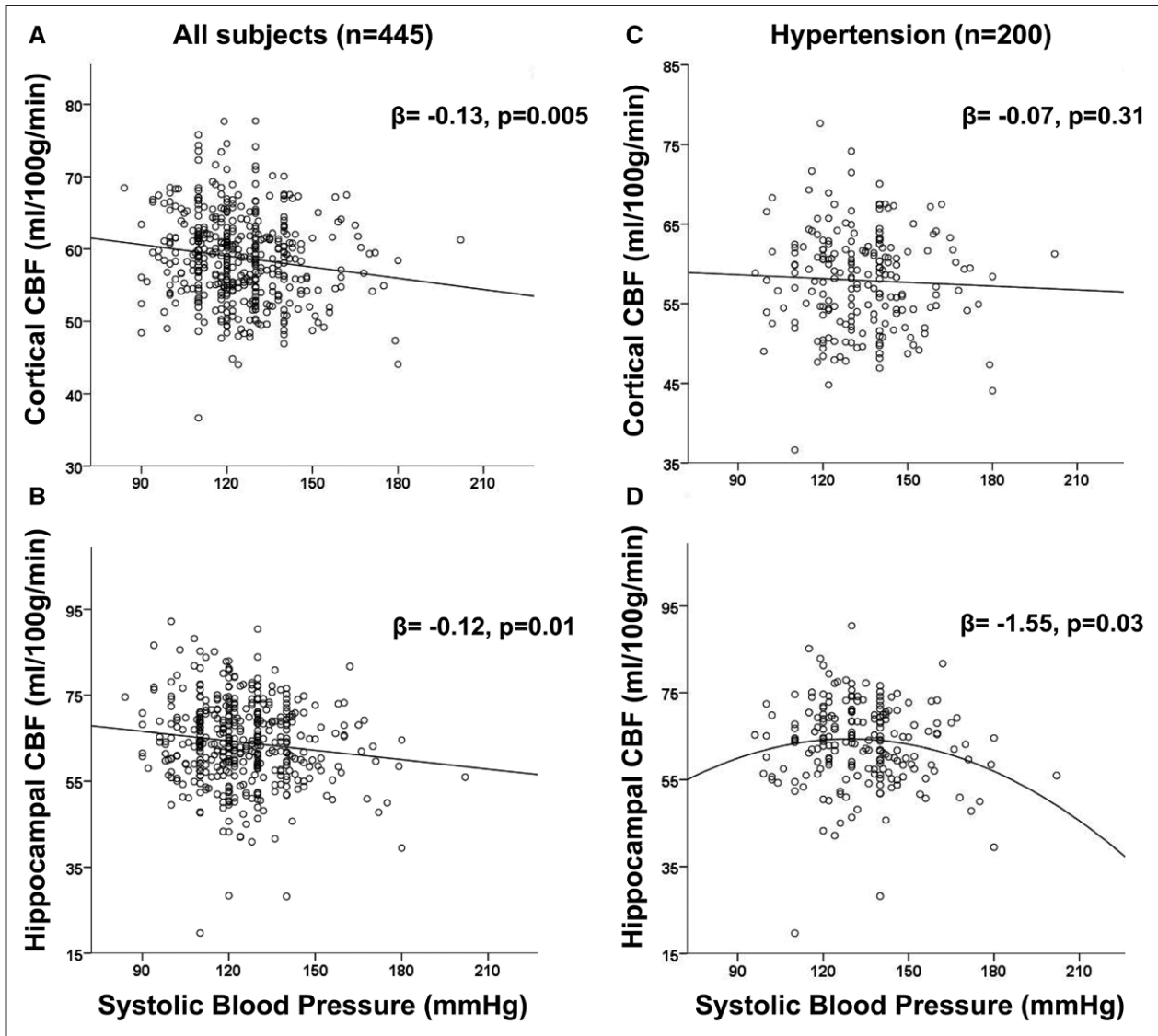
Figure 2. Cortical (**A**, **C**) and hippocampal (**B**, **D**) cerebral blood flow (CBF) as a function of systolic blood pressure in the entire group (**A**, **B**) and among hypertension patients (**C**, **D**). For **A**, through **C**, β values from linear regression model with sex included. For **D** from the model with statin use.

Analyses were conducted in the entire group, as well as in subjects with and without hypertension, separately.

Finally, to explore the relationship between BP and CBF changes over different baseline BP, we fit linear (first-order) and quadratic (second-order) polynomial surfaces to the 3-dimensional data of baseline BP, BP slope, and CBF slope, using the first 2 variables as inputs (x,y) and the last as output (z). Here, we have tested a parsimonious 4-parameter model:

$$z = p11xy + p10x + p01y + p00 \qquad (2)$$

which for our data appeared to have the same explanatory power as the general second degree model with 6 parameters:

$$z = p20x^2 + p11xy + p02y^2 + p10x + p01y + p00 \qquad (3)$$

The best model as indicated by Akaike information criterion was chosen. The surface fitting was performed using the Curve Fitting Toolbox in Matlab (ver. 2015a, Mathworks Inc). To estimate the baseline BP value marking the point where relationship between CBF slope and BP slope was changing, we calculated critical point (xc) from:

$$xc = \frac{p11 \times p01 - 2p10 \times p02}{4p02 \times p20 - p11^2} \qquad (4)$$

Linear models were checked for violations of model assumptions (distribution of the residuals, correct specification of the variance structure and linear relationship between the response and the linear predictor). If necessary, Box-Cox procedure was used to determine the most appropriate transformation of the variables. Violations were reported and models retested using transformed data. For all the analyses, the most parsimonious model was chosen, defined as including only significant or necessary (main effects when interaction was present) terms.

Statistical significance was defined as a *P* value <0.05. SPSS (version 23, SPSS, Inc, Chicago, IL) software was used for all analyses.

Results

The total sample of 445 subjects consisted of 61.6% women (age 68.4±7.7 years [mean±SD]; education 16.6±2.4 years); and 38.4% men (age 70.6±7.1 years; education 17.0±2.3 years; Table). The racial composition was 87.9% white, 8.8% black, 1.3% Asian, and 2% other races. In the longitudinal group of 185 subjects proportion of women (age 68.8±7.9 years; education 16.7±2.0 years) and men (age 71.2±5.9 years; education 17.2±2.2 years) was the same as in the entire sample. The

Table. Baseline Characteristics of the Entire Study Group (n=445

Variable	NTN (n=120)	Pre-HTN (n=125)	HTN (n=200)	P Value
Age, y	65.7±7.4	69.7±7.1*	71.0±7.1*	<0.001
Age range	50.1–82.3	51.9–87.9	51.1–91.2	
Education, y	16.8±2.3	16.7±2.1	16.7±2.5	0.90
Sex, n (% female)	88 (73)	76 (61)	110 (55)*	0.005
SBP, mm Hg	108.2±7.7	125.1±7.2	133.6±17.6	NA
DBP, mm Hg	66.1±7.3	74.8±7.8	77.2±11.0	NA
Mean arterial pressure, mm Hg	80.0±6.6	91.5±5.8*	95.9±11.6*†	<0.001
Pulse pressure, mm Hg	42.1±7.5	50.2±10.4*	56.4±14.6*†	<0.001
BMI*	24.6±4.0	26.1±4.4*	27.7±6.1*	<0.001
Total cholesterol,† mg/dL	203.7±33.2	196.2±35.2	187.7±35.3*	<0.001
High-density lipoprotein cholesterol,† mg/dL	70.0±19.9	64.5±17.6	60.6±15.6*	<0.001
Low-density lipoprotein cholesterol,‡ mg/dL	115.7±29.1	112.8±32.7	107.2±29.0*	0.04
Triglycerides,§ mg/dL	89.5±39.9	95.9±49.1	100.7±45.6	0.06
Glucose,‖ mg/dL	81.0±11.7	80.9±13.1	87.7±18.1*†	<0.001
Antihypertensive medication, n (%)	NA	NA	158 (79)	NA
Statins, n (%)	21 (17)	33 (26)	94 (47)*†	<0.001
Glucose-lowering medications, n (%)	1 (0.8)	2 (1.6)	17 (8.5)*†	0.001
GCHD risk,¶ %	5.2±3.7	8.2±4.1*	10.8±6.5*†	<0.001
Heart disease,# n (%)	5 (4)	4 (3)	24 (12)†	0.004
Cortical CBF,** mL/100 g per minute	60.0±0.54	58.8±0.52	58.1±0.41*	0.02
Hippocampal CBF,** mL/100 g per minute	64.9±0.87	64.1±0.85	63.6±0.67	0.49
Gray matter volume,†† % ICV	40.7±0.33	41.1±0.32	39.8±0.25†	0.005
Hippocampal volume,‡‡ % ICV	0.263±0.003	0.262±0.003	0.256±0.002	0.05
PWML,§§ n (%)	26 (22)	37 (30)	69 (35)*	0.04
DWML,§§ n (%)	17 (14)	24 (19)	50 (26)	0.05

Data are presented as mean±SD unless otherwise indicated. *P* values come from Kruskal-Wallis ANOVA or ANOVA (age). For categorical variables χ^2 was used. Post hoc comparisons are performed with Bonferroni correction. BMI indicates body mass index; BP, blood pressure; CBF, cerebral blood flow; DBP, diastolic BP; DWML, deep white matter lesion; GCHD, global coronary heart disease; HTN, hypertension; ICV, intracranial volume; NA, not applicable; NTN, normotension; PWML, periventricular white matter lesion; and SBP, systolic BP.

*n=435 (NTN=118, pre-HTN=122, and HTN=195).

†n=427 (NTN=119, pre-HTN=120, and HTN=188).

‡n=420 (NTN=114, pre-HTN=119, and HTN=187).

§n=426 (NTN=118, pre-HTN=120, and HTN=188).

‖n=429 (NTN=119, pre-HTN=121, and HTN=189).

¶n=419 (NTN=114, pre-HTN=119, and HTN=186).

#n=444 (NTN=120, pre-HTN=125, and HTN=199).

**Values presented as mean±SE, *P* values from ANCOVA after accounting for sex.

††n=444, (NTN=120, pre-HTN=124, and HTN=200), values presented as mean±SE, *P* values from ANCOVA after accounting for age, sex, and acquisition type.

‡‡n=442 (NTN=120, pre-HTN=124, and HTN=198), values presented as mean±SE, *P* values from ANCOVA after accounting for age, sex, and acquisition type.

§§n=437 (NTN=118, pre-HTN=124, and HTN=195), data presented as % subject rated as moderate or severe lesions (score of 2 or 3 on the Fazekas scale).

For comparison between groups:

*Different from NTN group at *P*<0.05 corrected.

†Different from pre-HTN group at *P*<0.05 corrected.

mean time between examinations was 2.2±0.51 years. Tables in the online-only Data Supplement list the characteristics of the longitudinal group alone (S1) and compared with subjects studied only at baseline (S2).

Relationships Between BP and CBF at Baseline

In the entire study group higher systolic BP (SBP) was associated with reduced cortical (β=−0.13, *P*=0.005 [B=−0.047, 95% CI, −0.080 to −0.015], entire model $F_{2,444}$=13.0, *P*<0.001,

sex included, Figure 2A) and hippocampal CBF (β=−0.12, P=0.01 [B=−0.069, 95% CI, −0.121 to −0.016], entire model $F_{2,444}$=7.1, P=0.001, sex included, Figure 2B).

Among subjects without hypertension (n=245), again, SBP was associated with reduced cortical (β=−0.15, P=0.02 [B=−0.078, 95% CI, −0.141 to −0.014], entire model $F_{1,244}$=5.8, P=0.02) and hippocampal CBF (β=−0.13, P=0.04 (B=−0.111, 95% CI, −0.217 to −0.005), entire model $F_{2,244}$=4.5, P=0.01, heart disease included).

Cortical CBF differed between the normotension, prehypertension, and hypertension subjects ($F_{3,444}$=4.2, P=0.02, after adjusting for sex). Normotension group had significantly higher cortical CBF than hypertension (P=0.01, 3% difference). Although CBF for prehypertension was in between normotension and hypertension values it did not differ from either group. Hippocampal perfusion did not differ between groups (Table).

Within the hypertension subgroup (n=200), there was no relationship between SBP and cortical CBF (Figure 2C). For the hippocampal CBF quadratic SBP^2 term was significant (β=−1.55, P=0.03 [B=−0.003, 95% CI, −0.006 to 0.000], entire model $F_{3,199}$=4.0, P=0.008, statin use included; Figure 2B). The analysis of transformed (squared) data confirmed the results (β=−1.53, P=0.03 [B=−0.18, 95% CI, −0.343 to −0.017], entire model $F_{3,199}$=4.1, P=0.008). The optimal SBP value calculated from Equation 1 was 125 mm Hg (see in the online-only Data Supplement).

Diastolic BP (DBP) was not related to CBF.

Longitudinal Relationship Between BP and CBF

In the longitudinal group (n=185) the interaction baseline SBP×SBP (F=12.8, P<0.001) was a significant predictor of CBF in the mixed model repeated measure. Thus, the relationship between change in SBP and change in CBF differed depending on the baseline SBP value. The model included sex, angiotensin receptor blockers, diuretics, and the presence of heart disease at baseline. Linear regression predicting the cortical CBF slope confirmed the results with a significant baseline SBP×SBP slope interaction (see in the online-only Data Supplement).

Further analyses showed that the relationship in the entire group was driven by the hypertension group, as there was no relationship between change in CBF and change in SBP in subjects without hypertension (n=106).

In the hypertension group (n=79) the mixed model repeated measure predicting cortical CBF confirmed the significant interaction baseline SBP×SBP (F=9.7, P=0.002). The model included angiotensin receptor blockers. Similarly, linear regression predicting the cortical CBF slope showed a significant baseline SBP×SBP slope interaction (see in the online-only Data Supplement). The best model corresponded to a simplified second-order polynomial that contained the x×y product (baseline SBP×SBP slope) and linear terms but in which x^2 and y^2 were null. The resulting model captures the key characteristics of our data: a positive correlation of SBP and CBF slopes (increased CBF with increased SBP) at low baseline SBP, a negative correlation of SBP and CBF slopes (increased CBF with decreased SBP) at high baseline SBP, and a smooth transition in the middle baseline SBP (Figure 3).

The xc calculated from Equation 4 revealed a saddle point in the fitted quadratic function and corresponded to 128 mm Hg (see in the online-only Data Supplement). Although the relationship between changes in SBP and changes in hippocampal CBF did not reach significance, we observed a similar pattern (Figure S3).

DBP changes were not related to CBF changes.

Additional data about the relationships between mean arterial pressure, pulse pressure and CBF changes, cerebrovascular resistance, and blood gases during image acquisition are presented in the online-only Data Supplement.

Discussion

Retrospective and epidemiological studies demonstrate the importance of adequate cerebral perfusion in healthy aging. Hypoperfusion has been suggested to lead to pathological and atrophic brain changes.[19,20] Unfortunately older studies suffered from limited resolution that confounds hypoperfusion and atrophy. In this prospective examination of a large cohort of normal aging, we have used high-resolution ASL-MRI to show that hypoperfusion is linked to high SBP. We found that cortical and hippocampal CBF declines with increasing pressure across the entire spectrum of BP. Although prehypertension group did not differ in CBF from normotensive subjects, a significant negative association between SBP and CBF was seen already when hypertension subjects were excluded from analyses. Moreover, CBF values in the prehypertension group were closer to hypertension, while their brain volumes were closer to volumes of subjects with normal BP. Our results strongly support the premise that CBF impairments precede structural changes because balanced steady-state free precession ASL method is minimally affected by partial volume effects. Our observations are in line with earlier studies showing that prehypertension confers higher risk of stroke as compared with lower BP[21] and suggest early treatment of elevated BP.

Based on increasing evidence from the literature it seems that impaired endothelial function and atherosclerotic changes in vessel walls cause reduced perfusion. The reduction in hippocampal perfusion may mediate a connection between hypertension and memory decline.

DBP was not related to CBF. This study supports the view that SBP is a more important vascular risk factor than DBP in subjects >50 years old.[2]

Statistical data modeling showed a quadratic relationship between hippocampal CBF and SBP in the hypertension group. Perfusion was maximized at around 125 mm Hg. This sweet spot was confirmed by longitudinal data, which revealed that moving away from the optimum SBP (128 mm Hg, not far from 125 mm Hg estimated from cross-sectional data) in both low and high BP direction was related to CBF reduction.

When SBP is above the optimum, hypoperfusion is likely caused by continued deleterious consequences of high BP: vascular wall hardening and narrowing. Recently Foster-Dingley et al[22] examined CBF in hypertensive (mean SBP=145 mm Hg) subjects in their 80s. Their finding of lack of CBF increase anticipated after a discontinuation of BP lowering treatment and consequent BP increase is consistent with our observations. The interpretation of hypoperfusion below the optimum in hypertension is more speculative. It is presumably caused
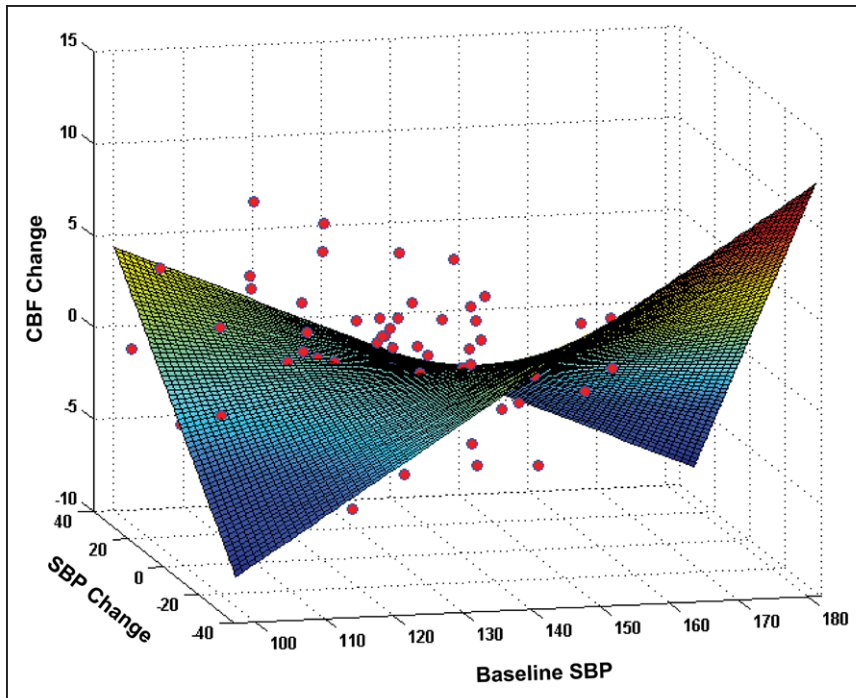
Figure 3. The results of 3-dimensional surface fitting depicting the relationship between baseline systolic blood pressure (SBP), change in SBP (slope: mm Hg/y) and change in cortical cerebral blood flow (CBF; slope: mL/100 g per minute per year). The graph shows a positive correlation of SBP and CBF slopes (increased CBF with increased SBP) at low baseline SBP and a negative correlation of SBP and CBF slopes (increased CBF with decreased SBP) at high baseline SBP.

by preexisting vessel damage resulting from previously high BP. It manifests as a failure of dilation in response to reduced perfusion pressure. Our results add to many previous reports that low BP or its sharp decline are linked in various populations to increased risk of dementia,[23] brain atrophy,[24] or poorer self-rating of mental and physical wellbeing.[25] They also corroborate the notion that BP lowering may not be beneficial in all instances and support the existence of much-debated optimal BP which would guarantee the best organ perfusion.

Reduction in vascular risk burden may be responsible for declining incidence of dementia.[26] It is known that that lower resting CBF predicts cognitive decline.[27] Our results suggest that perfusion improvement is a possible mechanism behind this risk reduction.

A quadratic relationship between SBP and CBF in the hypertension group was evident in the hippocampus but not in the neocortex. An earlier study showed that aging may be associated with increased vulnerability of posterior circulation to BP fluctuations.[28] Hippocampal blood supply comes mostly from the posterior cerebral artery.[29] Although the hippocampus has an arcade-like anastomosis system involving the anterior choroidal artery, this system is variable.[29,30] A study of patients with posterior cerebral artery occlusion showed that in subjects with better collateralizations, hippocampal infarct occurred less frequently.[31] This predominantly single artery supply or regional differences in cerebral autoregulation[32] may explain our results. Finally, the singularity of posterior circulation is also suggested by recent discovery showing that vertebral artery hypoplasia plays a role in triggering systemic hypertension to maintain adequate brain perfusion.[33]

We found that hippocampal perfusion was consistently higher than cortical CBF. This is consistent with recent findings of higher vascular density in the hippocampus as compared with the cortex.[34] It is also possible that spillover of ASL signal from big vessels passing near the hippocampus

(larger than penetrating arteries in temporal cortex) was the reason for this discrepancy. Despite our exclusion of voxels with CBF >150 mL/(100 g min; see Methods), the bias might have persisted.

There are several limitations of our study. First, our group was predominantly white with relatively low levels of vascular comorbidity, so generalizability is uncertain. Second, we did not have reliable information about the duration of hypertension. Third, subjects were assigned to the hypertension group based on baseline/screening in-office BP measurement. Should our hypertension group incorrectly include some subjects with white coat hypertension, the real difference between groups would have been even greater. Hypertension is a strong risk factor for stroke, which can affect CBF. We excluded subjects with clinically apparent or cortical stroke. As for WMLs, although their load was the highest in the hypertension group, the overall burden was low across all subjects. Throughout the article, we assumed that higher perfusion signifies better outcome. Some reports indicate that cognitive decline in associated with biphasic CBF changes, that is compensatory increase followed by CBF reduction.[35] Given that our group was cognitively stable, we think this possibility did not bias our results. Resting CBF is affected by many regulatory mechanisms. We could not control for all of them. We think, however, that large number of participants helps to overcome this potential problem.

Hippocampus, being a smaller structure, makes it more challenging to measure CBF. Higher variability of hippocampal CBF as compared with cortical values speaks in favor of this explanation. This variability could have bearing on our results by leading to type II error—failure to observe the relationship between BP and CBF—but it does not invalidate statistically significant findings. Validity of our results is also supported by increased recognition that CBF measured with ASL correlates well with gold standard $H_2^{15}O$ PET method.[36]

Finally, BP values where perfusion was the highest may differ from person to person and between different populations. Our results should rather be seen as a proof of concept that such point may exist than a fixed value ready to be applied in clinical settings.

Perspectives

In our group with relatively low vascular risk, cortical and hippocampal CBF decreased with increasing SBP across the spectrum of normal and high BP. In subjects with hypertension, there appeared to be a window of optimal mid-range SBP where brain perfusion was the highest.

Although more studies are warranted to replicate these findings and confirm the generalizability of the BP levels found in our group, our results have the potential to inform treatment goals for general and hypertensive populations.

Sources of Funding

Disclosures

None.

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Novelty and Significance

What Is New?

- We performed cross-sectional and longitudinal assessments of relationships between blood pressure (BP) and cerebral blood flow (CBF) in the neocortex and the hippocampus, a region associated with cognitive decline. Our observations add to earlier findings that high BP is related to reduction in brain perfusion but also indicate that among subjects with hypertension there may be an optimal BP which maximizes CBF.

What Is Relevant?

- Our results contribute to ongoing efforts to establish BP values and treatment goals for optimizing brain function.

Summary

Cortical and hippocampal CBF decreased with increasing systolic BP (SBP) across the entire BP spectrum and among subject without hypertension. Within the hypertension group, there was a quadratic relationship between SBP and hippocampal CBF ($\beta=-1.55$, $P=0.03$). The CBF was the highest in subjects with mid-range SBP around 125 mm Hg. Longitudinally, in hypertensive subjects CBF increased with increased SBP at low baseline SBP but increased with decreased SBP at high baseline SBP.