Cerebrovascular Support for Cognitive Processing in Hypertensive Patients Is Altered by Blood Pressure Treatment

J. Richard Jennings, Matthew F. Muldoon, Julie Price, Israel C. Christie, Carolyn C. Meltzer

Abstract—Hypertension is associated with mild decrements in cognition. In addition, regional cerebral blood flow responses during memory processing are blunted in parietal and thalamic areas among untreated hypertensive adults. Limited existing evidence supports all of these possibilities. We demonstrated that, compared with normotensive individuals, those with hypertension have damped regional cerebral blood flow response across task-related brain regions. Here, we test whether pharmacological treatment of hypertension normalizes regional cerebral blood flow responses and whether it does so differentially according to drug class. Treatment with lisinopril, an angiotensin-converting enzyme blocker, known to enhance vasodilative responsivity, was compared with treatment with atenolol, a β-blocker. Untreated hypertensive volunteers (n=28) were randomly assigned and treated for 1 year. Whole brain and regional cerebral flow responses to memory processing and acutely administered acetazolamide, a vasodilator, were assessed pretreatment and posttreatment. Peripheral brachial artery dilation during reactive hyperemia was also measured. Quantitative flow measures showed no difference in the magnitude of regional cerebral blood flow responses pretreatment and posttreatment to either memory tasks or acetazolamide injection. Brachial artery flow-mediated dilation increased with treatment. No differences between medications were observed. In brain regions active in memory processing, however, regional cerebral blood flow responses were more highly correlated after treatment. Specificity of cerebral blood flow to different regions appears to decline with treatment of hypertension. This greater correlation among active brain regions, which is present as well in untreated hypertensive relative to normotensive volunteers, may represent compensation in the face of less region-specific responsivity in individuals with hypertension. (Hypertension. 2008;52:65-71.)

Key Words: hypertension ■ cerebral blood flow ■ MRI ■ positron emission tomography ■ β-blocker ■ angiotensin-converting enzyme inhibitor

Mild-to-moderate hypertension is associated with minor deficits in cognition. Brain structure or function might account for these deficits. Cognitive processing elicits a regional redistribution of blood flow, providing metabolic support to active neural areas. Interference with this redistribution, blunting of regional blood flow, or structural loss because of poor perfusion might underlie the deficits of hypertensive individuals. Limited existing evidence supports all of these possibilities. We demonstrated that, compared with normotensive individuals, those with hypertension have damped regional cerebral blood flow (CBF; rCBF) responses in parietal and thalamic areas (regions of interest [ROI]) during working memory tasks and greater correlation among rCBF responses across task-related regions. Both observations might be because of a cerebrovascular adaptation to hypertension, most particularly, the remodeling of walls of small arteries, ie, thickening of the medial layer with or without a change in lumen diameter.

Antihypertensive medications have established influences on cerebral blood flow. Through its endocrine and paracrine actions, angiotensin promotes vascular remodeling and hypertrophy and also attenuates cerebral vasodilatory responses. Medications reducing angiotensin, eg, angiotensin-converting enzyme inhibitors (ACE-Is), generally reverse the peripheral vascular remodeling that occurs with hypertension, particularly when compared with β-blockers. Not all human studies, however, show reversal of remodeling with ACE-Is, and less is known about the impact of antihypertensive medications on cerebral circulation.

In the current investigation, we tested the hypothesis that treatment of hypertension with an ACE-I, lisinopril, as compared with a β-blocker, atenolol, alters remodeling and vasodilative capability and normalizes rCBF responses to working memory. Neither medication penetrates the blood brain barrier, thus, vascular effects are tested rather than any direct neural influence. Treatment effects on cerebral and peripheral vasodilatory reserve were assessed by acute administration of acetazolamide during quantitative CBF measurement and with brachial artery flow-mediated dilation, respectively.

Received January 13, 2008; first decision January 31, 2008; revision accepted May 1, 2008. From the Departments of Psychiatry and Psychology (J.R.J.), Department of Medicine (M.F.M.), Department of Radiology (J.P.), and the Department of Psychiatry (I.C.C.), University of Pittsburgh, Pa; and the Department of Psychiatry (C.C.M.), Emory University, Atlanta, Ga. Correspondence to J. Richard Jennings, E1329 WPIC, 3811 O’Hara St, Pittsburgh, PA 15213. E-mail: JenningsJR@upmc.edu © 2008 American Heart Association, Inc.

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Methods

Participants
A community sample was recruited from the greater Pittsburgh area via radio, television, newspaper, and health fairs. Participants were between 35 and 65 years of age and were required to have an average diastolic (fifth phase) blood pressure (BP) of 90 to 109 mm Hg, systolic BP of 140 to 179 mm Hg, or both. The restriction to middle-aged, mild-to-moderately hypertensive individuals was dictated by risk of our procedures and the likelihood that the reversibility of vascular remodeling might be higher in a relatively young, less hypertensive sample. BP was assessed after ≥5 minutes of rest using the ausculatory technique with a mercury manometer. The average of the last 2 of 3 readings done on 2 occasions defined BP. Participants had either no previous pharmacological treatment for hypertension or ≤6 months of BP medication within the past 5 years, with no BP medication taken in 6 months preceding enrollment. All of the participants provided informed consent, and the study was approved as ethical by the institutional review board of the University of Pittsburgh.

Physician-administered medical history and standard blood chemistry established medical eligibility. Participants were excluded for current use of cardiovascular or psychotropic medications or contraindication for use of an ACE-I or β-blocker, neurologic disorders, coronary heart disease (myocardial infarction or revascularization) or reported stroke, angina pectoris (determined by Rose questionnaire), a history of insulin-dependent diabetes, chronic renal insufficiency (serum creatinine >1.8 mg/dL), heavy alcohol consumption (≥24 standard drinks per week), consistent use of illegal drugs, absence of literacy in the English language (determined by self-report and ability to read consent documents), or inability to abstain from coffee, nicotine, or alcohol for a minimum of 4 hours before testing. Serum thyroid-stimulating hormone level was assessed in any participant reporting a history of thyroid abnormality. Those with known allergy to sulfa-containing antibiotics were included but did not undergo acetazolamide testing. These procedures excluded those with secondary hypertension because of renal failure, alcohol abuse, BP-raising drugs, and untreated thyroid disorders.

Design
Figure 1 illustrates the research protocol, participant flow, and participant withdrawal. Initial BP assessment, medical screening, self-report questionnaires, and detailed consent followed telephone screening. The next session included a second BP assessment and a neuropsychological examination. Separate sessions followed for brachial artery ultrasound, MRI, and positron-emission tomography (PET) examinations. All of the examinations were repeated after 1 year except for the screening and self-report instruments. This report focuses on 28 participants with complete quantitative rCBF measures. Participants were similar to noncompleting individuals in age, education, and personality factors; they differed in that continuing participants were significantly (χ² P<0.05) more likely to be male, white, and married. The University of Pittsburgh Institutional Review Board approved all of the procedures as consistent with ethical principles.

Medication Procedures
Patients were treated for 1 year within a randomized, double-blind design using either lisinopril (10 mg to 40 mg daily) or atenolol (25 mg to 100 mg daily). Medications were contained in unembossed capsules to ensure blinding. During a 6-week titration phase, drug dosage was gradually increased by 10 mg for lisinopril and 25 mg for atenolol. Participants were seen every 2 weeks for dosage adjustment and determination of BP, compliance, and adverse effects. Upward titration stopped if a participant’s BP had fallen to ≤135/85 mm Hg or if resting pulse fell to <50 bpm. If a participant’s BP remained >140/90 mm Hg on the full-dose treatment, 12.5 mg of hydrochlorothiazide was added (4 in lisinopril group and 7 in β-blocker group). Participants were withdrawn from the study if BP averaged >160/95 mm Hg on 2 consecutive visits during the maintenance phase (trimonthly visits, week 6 through the final visit at week 52). During visits, physical symptoms and quality of life were assessed by administering the Bulspitt Hypertension Questionnaire,23 and compliance was estimated based on returned pill counts.

Ultrasound Measurement of Endothelial Function
The influence of treatment on the capability for dilation of peripheral vessels was assessed with flow-mediated dilation of the brachial artery following standard methods.24,25 Brachial artery diameter was measured before and after reactive hyperemia induced by brachial occlusion for 4 minutes using a cuff inflated to 50 mm Hg above systolic BP. Brachial artery flow-related dilation assesses endothelium-dependent dilation related to the NO synthase and is impaired by hypertension.25,26

Structural MRI Measures
All of our subjects underwent a structural MRI using a GE Sigma 1.5T scanner to provide a structural image for mapping PET results and for the assessment of white matter hyperintensities. T2, fast fluid-attenuated inversion recovery, and spoiled gradient-recalled images were obtained (please see details in the data supplement available online at http://hyper.ahajournals.org). Severity of white matter hyperintensities was graded using a 10-point scale by 2 trained, experienced raters using standards developed for the Cardiovascular Health Study.27 Raters showed 90% agreement, and consensus ratings were analyzed. Participants with significant lacunar or other infarcts (n=2) were excluded from participation. These
were identified from the MRI films by a board-certified neuroradiologist. Significant infarcts were those judged to potentially influence functional images and/or to influence cognitive processing.

Functional PET Measures
Nine PET scans were performed to test rCBF responses during information processing (working memory tasks) and response to acetazolamide; please see details in the data supplement). Each of the memory tasks used the same display and 2 button responses. The “control memory” task required the subject to respond with the thumb if any letter appearing on the left of the screen and with the index finger for a letter appearing on the right of the screen. The “1-back memory” task required the subject to respond with the thumb if the spatial position of the letter currently appearing matched the spatial position that appeared immediately before it; otherwise the subject was to press with the index finger. The “2-back memory” task required the subject to respond with the thumb if the spatial position of the letter currently appearing matched the spatial position that appeared 2 times back. “Rest” and a “checkerboard/response” task (annular reversing checkerboard flickering at 8 Hz with right finger tapping) provided comparison conditions. Each task lasted 5 minutes and started 2 minutes before tracer injection. An intertask interval of ~5 minutes provided a break for the subject and permitted time for the preparation and delivery of the tracer. Checkerboard and rest tasks were presented only once and were randomized to be either the initial or final task of the cognitive battery, ie, scans 1 and 8. Each of the other tasks was presented twice with the order randomized, ie, scans 2 through 7. The cognitive battery was followed by the intravenous injection of a 13-mg/kg dose of acetazolamide, and the postabsorption scan followed after 20 minutes, ie, scan 9.39 Acetazolamide induces an extracellular acidosis and a resultant large, if not maximal, cerebral vasodilatory response acting through cyclooxygenase; the blood flow response to acetazolamide is impaired by hypertension.29–31

Quantitative CBF
The [15O]water data were analyzed using a 1-tissue compartment model.32-33 Model parameters corresponded with clearance of water from blood to brain (K1; mL/min per mL), brain-to-blood transfer (k2; min⁻¹), and an arterial input function timing delay (Δt). The 3 parameters were simultaneously determined using iterative least-squares curves fitting on a regional basis. K1 is a clearance parameter that is directly proportional to flow, and Kx×100 was used as a blood flow measure (mL/min per 100 mL).

ROIs were defined based on areas of differential participant/control activation from our initial study. The ROIs were regionally defined on the spoiled gradient recalled MRI for each participant and manually drawn using a version of the Imagentool software (CTI PET Systems). ROI placements for dorsolateral and ventrolateral prefrontal, parietal, amygdala/hippocampus, thalamic, cingulate, insula, and inferior frontal areas are shown in Figure S1.

Analysis
We tested the hypothesis that rCBF responses during memory processing would be enhanced by antihypertensive treatment with a repeated-measures ANOVA using the general linear model program within Statistica (StatSoft, Inc). Pretreatment and posttreatment were within-subject factors, and medication group was a between-subjects factor. Covariates were used to control for factors possibly influencing treatment response; because of the small sample size, age and gender were the only covariates routinely included in all of the analyses. Higher-order interactions with gender were not interpreted because of the small number of women per cell. Other possible confounders were added singly to check on their influence. The hypothesis of a greater impact on rCBF responses after treatment with lisinopril was tested with the pretreatment-posttreatment-by-medication-group interaction. We tested the hypothesis that correlations between activated brain areas would change with treatment by first determining the correlations of rCBF responses to working memory within prefrontal, posterior parietal, and amygdala/hippocampal ROIs before and after treatment. We then tested the difference between correlations using the Fisher z approach as implemented in Statistica. Two-tailed tests were uniformly used.

Table 1. Demographic Characteristics of Completing Participants

<table>
<thead>
<tr>
<th>Medication Group</th>
<th>Lisinopril (ACE-I), n=20</th>
<th>Atenolol (β-Blocker), n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.9 (5.6)</td>
<td>51.3 (7.4)</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>70</td>
<td>83</td>
</tr>
<tr>
<td>Race, % white</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.5 (4.9)</td>
<td>29.5 (4.7)</td>
</tr>
<tr>
<td>Education, % more than high school</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>Married, %</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>203 (34)</td>
<td>214 (31)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>98 (20)</td>
<td>96 (30)</td>
</tr>
<tr>
<td>Drink alcohol &gt;1 or 2 times per year, % of group</td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td>Average No. of cigarettes per day</td>
<td>2 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Sulcus size rating</td>
<td>3.0 (0.8)</td>
<td>2.8 (0.9)</td>
</tr>
<tr>
<td>Ventricle size rating</td>
<td>2.2 (0.6)</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td>White matter rating</td>
<td>1.3 (0.8)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Medication compliance, % 97 (8)</td>
<td>98 (2)</td>
<td></td>
</tr>
</tbody>
</table>

Data show arithmetic mean (SD) unless otherwise specified. Groups were compared by independent t tests or χ²; no statistically significant differences were observed between medication groups.

Results

Participant Characteristics
The participants, as classified by their assignment to medication, were comparable, showing no statistically significant differences, although numeric differences were present for gender, race, education, and smoking history (Table 1). Heart rate, BP, and vascular distensibility for the 2 groups were comparable pretreatment (Table 2). F-values from the ANOVA are presented for baseline differences between groups, pretreatment and posttreatment, and pretreatment and posttreatment by medication group factors. All of the variables changed with treatment, but only heart rate changed differentially as a function of treatment group. Atenolol lowered heart rate more than lisinopril.

CBF and rCBF
Treatment of hypertension with either drug maintained pretreatment values for estimated CBF, rCBF, and changes in these measures elicited by the working memory task (Table 3). In contrast to our hypothesis, the working memory tasks did not elicit a greater rCBF response after 1 year of antihypertensive treatment. The results tabulated are for the posterior parietal ROI; in our previous work, this area was shown to have decreased rCBF response in hypertensive subjects relative to normotensive subjects. This area is representative of all of the ROI results, including overall CBF. The posterior parietal results show an effect of increasing memory load (F(2,18)=18.1; P<0.001) but no treatment effect (F(1,23)=1.1; P not significant) or treatment by medication group interaction (F(1,23)=0.0; P not significant).
Cerebral dilation in response to acetazolamide was unaffected by treatment ($F_{1,11}=0.0$; $P$ not significant) and did not show a treatment by medication interaction ($F_{1,11}=0.7$; $P$ not significant). Essentially the same results were obtained if patients receiving supplementary hydrochlorothiazide were excluding from the analyses. Similarly, the addition of covariates individually failed to alter the statistical significance of any of the terms in the analysis and also failed to show significant covariate effects. Those tested were white matter load, smoking, alcohol use, education level, body mass index, estimated intelligence, depression, and systolic BP response to treatment.

**Peripheral Vasodilative Effects**

An analysis of maximal brachial artery dilation after occlusion, covarying initial artery diameter, indicated an increase in dilation after treatment for both medications (see Table 2). No difference between medications was observed. The increase in the percentage of dilation after 1 year of treatment was inversely correlated with change in brachial artery dilation.

**Correlation of Regional Responses**

Finally, we examined correlations between rCBF responses in regions known to be involved in working memory processing. The magnitude of the correlations increased significantly after 1 year of antihypertensive treatment (Table 4 and Figure 2). Correlations did not differ between medication groups.

**Discussion**

This experiment had 2 important outcomes. The first outcome was the absence of any difference in cerebrovascular treatment effects between ACE-I and β-blocker medication. We assumed that ACE-I treatment would be superior to β-blocker treatment for reversing any remodeling of cerebral vessels, restoring cerebral vasodilative responsivity, and enhancing greater specificity of response among brain areas during cognitive processing. Our results suggested that these assumptions were oversimplifications. The second outcome was an increase in correlation of rCBF responses between memory-related regions after successful BP treatment. We had found previously that rCBF increases during memory in different activated brain regions were more highly correlated among hypertensive relative to normotensive individuals; standard antihypertensive treatment increased these correlations.

The increase in correlation among brain areas after treatment indicates altered cerebrovascular support for memory processing, eg, rCBF response during working memory in one region, eg, prefrontal cortex, can be predicted more accurately from rCBF dilation response to acetazolamide within the brain areas before treatment. Posterior parietal, dorsolateral prefrontal, and amygdala/hippocampal areas were tested for the

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**Table 2. Initial and Treated Mean Values (SEs) of BPs, Heart Rate, and Peripheral Vascular (Brachial Artery) Dilation and ANOVA Results**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>F-Value</th>
<th>P Value</th>
<th>F-Value</th>
<th>P Value</th>
<th>F-Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>148.7 (3.2)</td>
<td>127.0 (3.6)</td>
<td>0.1</td>
<td>ns</td>
<td>72.2</td>
<td>&lt;0.001</td>
<td>0.3</td>
<td>ns</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>93.3 (2.6)</td>
<td>79.3 (2.7)</td>
<td>1.2</td>
<td>ns</td>
<td>78.5</td>
<td>&lt;0.001</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.4 (2.8)</td>
<td>66.8 (2.7)</td>
<td>1.9</td>
<td>ns</td>
<td>27.6</td>
<td>&lt;0.001</td>
<td>6.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>148.7 (2.7)</td>
<td>127.0 (2.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.4 (2.8)</td>
<td>66.8 (2.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery dilation, %</td>
<td>4.4 (1.0)</td>
<td>7.1 (1.0)</td>
<td>0.1</td>
<td>ns</td>
<td>7.6</td>
<td>&lt;0.01*</td>
<td>0.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

See text for description of analyses; age and gender were used as covariates in these analyses.

*$F_{1,20}=7.4$ and $P=0.01$ for percentage of vascular dilation uncorrected for initial baseline.

**Table 3. rCBF Estimates (mL/min per 100 mL) Within the Posterior Parietal ROI for the Different Task Conditions Pretreatment and Posttreatment**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril Group (n=12)</td>
<td>48.0 (2.7)</td>
<td>47.2 (2.6)</td>
<td>44.2 (1.8)</td>
<td>39.9 (1.7)</td>
</tr>
<tr>
<td>Atenolol Group (n=16)</td>
<td>49.0 (4.0)</td>
<td>51.1 (3.7)</td>
<td>42.6 (2.6)</td>
<td>42.0 (2.4)</td>
</tr>
<tr>
<td>Rest</td>
<td>Control memory</td>
<td>44.2 (2.6)</td>
<td>44.5 (2.3)</td>
<td>43.0 (2.4)</td>
</tr>
<tr>
<td>Checkerboard</td>
<td>46.7 (3.0)</td>
<td>44.4 (2.7)</td>
<td>44.4 (2.7)</td>
<td>42.5 (1.9)</td>
</tr>
<tr>
<td>1-back</td>
<td>Acetazolamide*</td>
<td>49.2 (3.3)</td>
<td>46.4 (2.9)</td>
<td>46.4 (2.9)</td>
</tr>
<tr>
<td>2-back</td>
<td>57.5 (4.2)</td>
<td>53.4 (4.2)</td>
<td>59.6 (3.2)</td>
<td>59.6 (3.0)</td>
</tr>
</tbody>
</table>

Means (SEs) are given; CIs for 95% of the possible means may be approximated assuming normality by multiplying the SE by ±2. There are no statistical differences between medication groups or pretreatment-posttreatment (see text).

*n for acetazolamide data is 9 for the lisinopril group and 13 for the atenolol group.
motensive participants.37 lower in long-term treated, older hypertensive relative to normotensive individuals.38,39; (2) compensatory changes within hippocampal circuits are documented in the animal literature40; and (3) enhanced posttreatment correlations were not maladaptive in that cognitive performance was maintained or increased across our treatment period (data not shown). Our measures lack the resolution, however, to specifically relate our results to those in the animal literature (in which compensation can more readily be demonstrated). Longitudinal research with larger samples will be required to assess whether the observed changes are compensatory or, perhaps, even deleterious for some functions.

Our interpretation must be tentative absent further knowledge of the mechanism inducing increased correlation among regions after treatment. Our results show that quantitative, global CBF was maintained despite a significant fall in BP. Presumably this reflects cerebral autoregulation with flow held constant via a decrease in vascular resistance.41 This possibility is consistent with previous observations, eg, that of Lipsitz et al.,42 of ACE-I treatment heightening both CBF velocity and carotid artery distensibility. The increased correlation between the rCBF responses in activated regions with treatment may be a consequence of dilated resistance vessels that are less responsive to variations in metabolic debt in the different regions active in a task.43 This interpretation seems reasonable, as our measures show an absence of vasodilative responsivity of cerebral vessels, heightened brachial artery dilative responsivity posttreatment, and an inverse correlation between these measures. However, clearly different dilative mechanisms and vessel types are probed by brachial artery flow-mediated dilation and dilation induced by cognitive performance and acetazolamide.22,26,29,31

Thus, our interpretation is limited by differences between vasodilative mechanism in peripheral and central circulations, differences in sensitivities of these mechanisms within small and large vessels, and the variety of vasodilative mechanisms in general.34,44–47

This complexity of vasodilative mechanisms is highlighted by our incorrect initial assumption of a greater cerebrovascular efficacy of ACE-Is relative to β-blockers. ACE-Is are known to successfully reverse hypertensive vascular hypertrophy and re-

### Table 4. Correlation of rCBF Responses to 2-Back Working Memory Task Among Prefrontal, Parietal, and Amygdala/Hippocampal ROIs

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Pretreatment (n=28)</th>
<th>Posttreatment (n=28)</th>
<th>Significance of Difference, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal to parietal</td>
<td>0.62*</td>
<td>0.94*</td>
<td>0.006</td>
</tr>
<tr>
<td>Prefrontal to amygdala/hippocampus</td>
<td>0.58*</td>
<td>0.84*</td>
<td>0.05</td>
</tr>
<tr>
<td>Parietal to amygdala/hippocampus</td>
<td>0.42*</td>
<td>0.80*</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Pretreatment correlations show a similar pattern when participants with PET data only for the pretreatment are added to the calculation (to yield n=43) and the significance of the pretreatment to parietal correlation difference remains (P=0.002). Removal of 1 participant with extreme change scores reduces the amygdala/hippocampus differences to a trend, but the difference between pretreatment/posttreatment correlation differences remains significant (P=0.04).

*P<0.01.

following reasons: (1) these areas showed differences in correlation between hypertensive and normotensive groups in our initial study;2 (2) rCBF in these areas changes during memory performance, increasing in dorsolateral and posterior parietal areas and decreasing in amygdala/hippocampus in our work7 and that of others;35,36, and (3) posterior parietal and amygdala/hippocampus rCBF changes are related to memory performance.35,36 Different cognitive tasks typically elicit rCBF responses that redistribute existing CBF to brain regions of which the activation is associated with successful performance of the particular task.9 We previously interpreted increased concomitance of rCBF response across regions among hypertensive relative to normotensive individuals as a compensation for less robust rCBF response among hypertensive individuals in their thalamic and posterior parietal regions.7 Treatment appeared to facilitate or, at least, not alter such compensation, because correlations of rCBF responses across brain regions increased with treatment. Note that our findings are for responsivity of rCBF to cognitive load. Indeed, regional correlations of glucose metabolism at rest between brain regions have been shown to be lower in long-term treated, older hypertensive relative to normotensive participants.37

Pre Treatment Correlation of Response to Memory Task between Parietal and Prefrontal ROI's

Post Treatment Correlation of Response to Memory Task between Parietal and Prefrontal ROI's

Figure 2. Scatter diagrams of the relationship between dorsolateral prefrontal and posterior parietal areas before and after treatment. Data from 1 extreme participant is omitted; pretreatment correlation=0.61; posttreatment correlation=0.86.
An increase in vasodilative capacity of the brain after ACE-I treatment, however, has been an equivocal finding. Our results showed that antihypertensive treatment increased vasodilative response in the brachial artery but not in cerebrovascular vessels. The increase in endothelium-dependent vasodilation in the peripheral circulation after successful BP lowering, irrespective of type of medication, has been reported, although typically ACE-Is are superior to other medications. The failure to show a parallel influence in the cerebral circulation is consistent with observations that acetazolamide acts through cyclooxygenase rather than the NO synthase pathway induced by flow-induced dilation, and dilation via this pathway has been reported to be unaltered in hypertension and uninfluenced by its treatment in animal models. Assessment of vasodilative changes with quantitative blood flow measures is a strength of our study, but we did not assess velocity measures, other measures of flow, or blood volume. Our understanding of the cerebrovascular response to hypertension treatment requires greater attention to vessel characteristics and vasodilative mechanisms, as well as converging measurement approaches that were not feasible in the current investigation. Finally, the role of eutrophic versus hypertrophic remodeling and the importance of reversing this in the cerebral circulation also requires further consideration, particularly given suggestions that vasodilative capacity and characteristics of remodeling are unrelated.

Our study has significant limitations. Sample size was modest, reflecting the invasiveness of our measures and difficulty recruiting untreated hypertensive participants. Statistical power was sufficient only to detect relatively large, clinically significant effects. Furthermore, women withdrew from testing more than men. This threatens generalization from our study. We only studied 2 medications; others might act differently. In particular, an angiotensin II receptor blocker might be more effective than the current ACE-I in altering cerebral function. Severe cerebrovascular disease appears to alter the coupling between blood flow and neural activation. If this coupling is also disrupted at moderate levels of hypertension, our interpretation of rCBF as an indicator of neural activation is threatened. Peripheral BP response to our memory tasks might directly alter the rCBF signal, but this appears unlikely given the current, modest magnitude of the peripheral BP response. Finally, the absence of an untreated or placebo control group means that we cannot directly assess the possibilities of influence of our results because of time, a continuing hypertensive disease process, or practice effects.

**Perspectives**

Loss of specificity of rCBF with hypertension that is further magnified by treatment may have implications for vulnerability to stroke and cognitive decline. Individuals with low rCBF to one area have a greater tendency to show low rCBF to all of the active processing areas after treatment. Future work will be required to test whether this creates a vulnerability to future vascular and neuropsychiatric diseases or is an appropriate compensatory adjustment to the minimal loss of cognitive function associated with hypertension.

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**Disclosures**

None.

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J. Richard Jennings, Matthew F. Muldoon, Julie Price, Israel C. Christie and Carolyn C. Meltzer

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