Cerebral Blood Flow in Hypertensive Patients
An Initial Report of Reduced and Compensatory Blood Flow Responses During Performance of Two Cognitive Tasks

J. Richard Jennings, Matthew F. Muldoon, Christopher M. Ryan, Mark A. Mintun, Carolyn C. Meltzer, David W. Townsend, Kim Sutton-Tyrrell, Alvin P. Shapiro, Stephen B. Manuck

Abstract—We asked whether the altered cerebral vasculature associated with essential hypertension might dampen or redirect the regional cerebral blood flow (rCBF) response to cognitive work. Relative rCBF was assessed with [$^1^5$O]water positron emission tomography during a working memory task, a memory span task, and two perceptual control tasks. Unmedicated hypertensive patients and control subjects differed in rCBF response during both memory tasks. Hypertensives showed relatively diminished rCBF responses in right hemisphere areas combined with compensatory activation of homologous areas in the left cerebral cortex. Essential hypertension appears to selectively influence the circulatory reserve of portions of cerebral cortex and secondarily induce recruitment of other cortical areas to process certain tasks. (Hypertension. 1998;31:1216-1222.)

Key Words: hypertension, essential blood flow neuropsychology tomography, emission-computed memory attention

The cerebral blood vessels of chronically hypertensive patients have an increased vascular resistance that offsets high systemic pressures and maintains global CBF at near normal levels. Histologically, cerebral parenchymal arterioles show a thickened media and a narrowed lumen. Such changes may reduce the vasodilatory capability of cerebral vessels and thereby limit maximum delivery of oxygen and nutrients to active brain tissue. Cognitive work raises metabolic demand in activated regions of the brain, necessitating concomitant local changes in blood supply. Because of their compromised vasodilatory capacity, we hypothesized that patients with untreated high blood pressure would manifest less rCBF response than control subjects in brain areas activated by cognitive tasks and that these subjects might adopt different, presumably compensatory, topographical patterns of rCBF response.

Methods

Case Selection
Nine unmedicated hypertensive individuals were compared with five control subjects who were similar in mean age (hypertensive, 60 to 67 years; control, 59 to 68 years), education (14 versus 16 years), and gender (88% male versus 62% male) but differed in blood pressure (151/91 mm Hg versus 120/76 mm Hg). Hypertension was defined as two consecutive clinical screenings with systolic pressures between 140 and 180 mm Hg and diastolic pressures between 90 and 135 mm Hg. Normotensive status was similarly determined as systolic pressures <135 mm Hg and diastolic pressures <85 mm Hg. Hypertensive patients were unmedicated (for a minimum of 8 weeks) and had less than a 2-year lifetime history of taking any hypertensive medication. Exclusion criteria included secondary hypertension; use of any cardiovascular or psychiatric medication; cerebrovascular disease (by report, magnetic resonance imaging, and carotid ultrasound); and history of myocardial infarction, diabetes, cancer, psychiatric disease/alcoholism, or renal and pulmonary disease. One patient reported significant use of his left hand, while other patients reportedly being consistently right-handed. The results reported were essentially unchanged, however, when analyses were repeated without this subject. Informed consent was obtained from all subjects after the nature and possible consequences of participation were explained (following procedures approved by the Institutional Review Board of the University of Pittsburgh).

Cognitive Tasks
Two tasks were selected that were known to elicit consistent rCBF responses. Each task was presented at two levels of difficulty. (1) A continuous performance task required subjects to detect the letter “x” in a stream of letters (CPTx); at a higher level of difficulty, the subject responded to any letter that was a repeat of that letter at a position one removed (CPTskip). The CPT was presented on a video screen controlled by a Macintosh IIci computer. Letters were presented for 500 milliseconds each, separated by a 2500-millisecond interval. In the CPTx task, the subjects were instructed to press the button whenever they saw an “x.” In the CPTskip task, the subjects were instructed to press the button whenever a letter was repeated with exactly one intervening nonidentical letter (eg, B Z B, but not BB or B C Z B). (2) An auditory free recall task required the subject to remember and repeat back single words; at a higher level of difficulty, the subjects were instructed to press the button whenever a letter was repeated exactly. Twelve words were presented and then repeated back. With use of a tape recorder, the single-word task presented high-frequency nouns at a rate of one per second. Recall (basically word repetition) occurred immediately after each single item. This task was compared with the 12-word task in which 12 words were presented at a rate of one per second followed by a 15-second pause during which the

Received December 15, 1997; first decision December 31, 1997; revision accepted January 9, 1998.
From the University of Pittsburgh (Pa).
Correspondence to J.R. Jennings, E1329 WPIC, 3811 O’Hara St, Pittsburgh, PA 15213.
E-mail injenn@vms.cis.pitt.edu
© 1998 American Heart Association, Inc.
volunteers repeated back verbally in any order as many words as possible. Two perceptual tasks were used: visual fixation of a crosshair display and visual observation of a checkerboard pattern alternating colors at a 6-Hz frequency.

**Imaging Methods**

All PET scans were acquired in three-dimensional mode (septa retracted) on an ECAT 951R/31 scanner (Siemens/CTI PET Systems). The 951R scanner covers an axial field of 10 cm with a spatial resolution of 6.5 mm, full width at half maximum. A 15-minute transmission scan was collected to provide coefficients for attenuation correction of the emission data. Each activation task was begun 15 seconds before the injection of 7 mCi of $^{15}O$ water, and the emission scan was begun 30 seconds after injection, for a scan duration of 60 seconds. No background frame was acquired. All scans were reconstructed in three dimensions without scatter correction and with a pixel size of 1.7 mm, using a Hanning smoothing window and a 0.8 Nyquist cutoff frequency. A total of 12 emission scans were acquired with an 8-minute interval between injections to allow for the decay of the $^{15}O$ water. For each subject, 12 scans were performed with a fixed task order: word repetition, 12-word free recall, checkerboard display, CPTx, CPTskip, visual fixation, CPTskip, CPTx, checkerboard, 12-word free recall, word repetition, and visual fixation. Correction for head movement during the study was made by realigning the images using the Automated Image Registration (AIR) package. Images were then converted into the stereotactic coordinate system of a standard brain atlas. No measurements of absolute global flow were made then converted into the stereotactic coordinate system of a standard brain atlas.

**Results**

Performance was comparable between groups and generally good: on the CPTs, hypertensive patients averaged 87% correct and control subjects 74%; on the free recall tasks, hypertensives averaged 70% correct, controls 66%. Despite the absence of group differences, the range of individual performance scores required us to ensure that rCBF activation differences between groups were not due solely to differences in performance between individuals. To check this possibility, the percentages of correct scores, as well as reaction time and false-alarm rates from the CPTs, were correlated to rCBF values at areas showing significant differences between groups (see Table 2). No significant correlations were observed. Furthermore, covarying performance did not influence the statistical significance of results in the analyses presented below.

Changes in rCBF during performance were first examined separately for patients and control subjects. Hypertensive patients responded with rCBF changes primarily in left hemispheric areas in the analyses comparing levels of difficulty for both CPT and free recall. In contrast, control subjects showed primarily right hemispheric rCBF responses during performance of both tasks. Table 1 shows that controls activated right frontal, prefrontal, parietal, and temporal areas in both tasks.

Hypertensive patients responded with left parietal and frontal rCBF during the CPT and showed trends toward left frontal, temporal, prefrontal, and parietal rCBF responses in the free recall task.

Table 2 shows the statistical results from direct comparison of the two groups on how much their rCBF response increased with increasing task difficulty for the two cognitive tasks. For the CPT, both right frontal and parietal rCBF responses were significantly greater in controls than in hypertensives. Figure 1 shows these results as Z score maps of brain slices and as a graph of mean rCBF responses by group and task level. The brain slices illustrate the extent and statistical strength of the rCBF changes that were greater in controls than in hypertensives. The figures shows horizontal sections at 8-mm intervals beginning at a z value of 12 mm in the Talairach and Tournoux nomenclature, 12 mm above the anterior commissure–posterior commissure line. The slices are shown until $z=36$ mm and illustrate the relatively large extent of the differences in parietal and frontal cortex between groups in the change in rCBF with CPT difficulty. The right panel of Figure 1 shows the mean across subjects of the rCBF counts for the different levels of CPT difficulty. The counts are taken from the centroid of the area of activation as reported by the SPM program and thus correspond directly to the results shown in Table 2. The upper graph corresponds...
to the parietal activation (the \(x\) and \(y\) values can be referred to the slices with \(x=0\) defined by the midline and \(y=0\) defined by the vertical traversing the posterior margin of the anterior commissure). The lower graph corresponds to the frontal activation. Both figures show a robust increase in rCBF change for control subjects but little change for hypertensives. In addition, both figures indicate that relative rCBF in the hypertensives is higher than that of the controls at rest but

### TABLE 1. Areas With 50 or More Activated Voxels Associated With Z > 3.25 (Uncorrected \(P < 0.001\)) for CPT and Free Recall Task

<table>
<thead>
<tr>
<th>Area</th>
<th>Brodmann Area</th>
<th>(x, y, z, \text{mm})</th>
<th>Region Size, voxel</th>
<th>(Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Right prefrontal, frontal, Broca’s</td>
<td>9, 44, 46</td>
<td>26, 28, 28</td>
<td>2908</td>
</tr>
<tr>
<td></td>
<td>Right parietal</td>
<td>39</td>
<td>36, -50, 28</td>
<td>955</td>
</tr>
<tr>
<td></td>
<td>Right temporal</td>
<td>21</td>
<td>-52, 34, -4</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Left parietal</td>
<td>40</td>
<td>-50, -54, 36</td>
<td>234</td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td>Left parietal</td>
<td>40</td>
<td>-36, -54, 40</td>
<td>854</td>
</tr>
<tr>
<td></td>
<td>Right occipital</td>
<td>19</td>
<td>30, -66, 40</td>
<td>672</td>
</tr>
<tr>
<td></td>
<td>Left frontal/somatomotor cortex</td>
<td>6, 8</td>
<td>-34, 4, 52</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Right frontal, Broca’s</td>
<td>44</td>
<td>44, 12, 32</td>
<td>337</td>
</tr>
<tr>
<td></td>
<td>Left prefrontal</td>
<td>10</td>
<td>-34, 50, -4</td>
<td>85</td>
</tr>
<tr>
<td><strong>Free recall task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Right prefrontal</td>
<td>9</td>
<td>36, 24, 28</td>
<td>834</td>
</tr>
<tr>
<td></td>
<td>Right parietal</td>
<td>40</td>
<td>50, -50, 32</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>Occipital</td>
<td>18</td>
<td>0, -66, 20</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Right frontal</td>
<td>6</td>
<td>10, 16, 52</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>Right temporal</td>
<td>21</td>
<td>54, -40, 0</td>
<td>235</td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td>Left frontal</td>
<td>6</td>
<td>-28, 0, 52</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>Left temporal</td>
<td>21</td>
<td>-60, -20, -12</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>Left prefrontal</td>
<td>46, 9</td>
<td>-38, 42, 16</td>
<td>940</td>
</tr>
<tr>
<td></td>
<td>Left parietal</td>
<td>39</td>
<td>-38, -66, 36</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td>Right putamen</td>
<td>26, 12, 4</td>
<td>133</td>
<td>3.53</td>
</tr>
</tbody>
</table>

*Areas showing statistical significance (\(P\leq 0.05\) by corrected statistic \(P(Z_{\text{max}})\)) from SPM.

### TABLE 2. Areas With 50 or More Contiguous Activated Voxels (Z > 3.25, Uncorrected \(P < 0.001\)) That Differed Between Patients and Controls During Performance of CPT or Free Recall Task

<table>
<thead>
<tr>
<th>Area</th>
<th>Brodmann Area</th>
<th>(x, y, z, \text{mm})</th>
<th>Region Size, voxel</th>
<th>(Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls-&gt;hypertensive patients</td>
<td>Right frontal, prefrontal, Broca’s</td>
<td>9, 44, 46</td>
<td>26, 22, 24</td>
<td>1929</td>
</tr>
<tr>
<td></td>
<td>Right posterior parietal</td>
<td>40</td>
<td>36, -44, 28</td>
<td>908</td>
</tr>
<tr>
<td>Hypertensive patients-&gt;controls</td>
<td>Left hippocampus</td>
<td>-18, -32, -4</td>
<td>432</td>
<td>4.14*</td>
</tr>
<tr>
<td></td>
<td>Left prefrontal</td>
<td>9, 10</td>
<td>-26, 48, 8</td>
<td>115</td>
</tr>
<tr>
<td><strong>Free recall task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls-&gt;hypertensive patients</td>
<td>Right temporal</td>
<td>37</td>
<td>44, -46, -8</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Right prefrontal</td>
<td>46</td>
<td>44, 30, 4</td>
<td>311</td>
</tr>
</tbody>
</table>

*\(P<0.05\) by corrected \(Z\) value \(P(Z_{\text{max}})\).
not during task performance. Differences in rCBF for the free recall tasks were not significant after correction for number of comparisons; however, controls showed a similar trend for enhanced right hemispheric prefrontal and temporal rCBF response relative to little change in rCBF response for hypertensives.

Hypertensive patients might be expected to show greater left hemisphere responses than control subjects given the results from the separate analyses within each group. However, this was not seen in the contrast specifically testing for areas in which hypertensives showed greater rCBF change than controls. Table 2 shows that only a left hippocampal (x = −18, y = −32, z = −4) rCBF response showed a statistically significant difference favoring hypertensives relative to controls. Figure 2, constructed similarly to Figure 1, shows slices at z = −8 to z = 0 that largely encompass the area yielding the group difference. The accompanying graph for the hippocampal rCBF differences shows that the result is primarily due to a drop in hippocampal rCBF response in controls during the processing of the CPTskip; hypertensive patients maintained a similar rCBF response across CPT difficulty. Table 2 does show a trend for greater left prefrontal rCBF response in hypertensives relative to control subjects; means for this comparison (not shown) demonstrated a greater change in rCBF for hypertensives relative to controls during the CPTskip. Overall, the results show a pattern of memory performance associated with robust right hemispheric prefrontal, parietal, and temporal rCBF response in controls. This response is dampened in hypertensives. Hypertensive patients show little differential response to tasks of differing difficulty but show significant left hemispheric rCBF responses not present in controls. The left hemispheric activations are modest in that we could not show the differences in rCBF responses across task difficulty to be statistically larger in left hemispheric areas of hypertensives relative to controls.

No significant differences in rCBF response or lateralization were observed for a perceptual task (viewing an alternating checkerboard pattern). Both groups bilaterally increased occipital rCBF in response to the checkerboard pattern: controls, 4237 voxels with a centroid at 8, −98, and 4 [Z = 6.50, P(Z_{max}>u) < 0.001]; hypertensives, 3631 voxels.
with a centroid at $-16, -100, \text{and~} 0 \ [Z=7.21, \ P(Z_{\max}>u)<0.001]$. The absence of differences between hypertensive and control rCBF responses in the visual checkerboard task suggests that lateralization is task- or brain region–specific rather than a general property of hemisphere perfusion in hypertensives.

**Discussion**

We have investigated the rCBF response to a verbal episodic memory task and a sustained attention task with an added working memory component. Both tasks were challenging to our participants, and we, as well as earlier investigators, found significant rCBF changes in response to the tasks. The most important difference between hypertensive and control participants was a decreased responsivity to increased task difficulty among hypertensives. An unexpected further difference was in the lateralization to different hemispheres of the primary task-induced changes between hypertensive and control subjects. The unanticipated nature of this finding and the relatively low number of participants in the present study indicate the need for replication of the present results.

Because we sought to show that hypertensive volunteers differed from control subjects in rCBF, it is important to demonstrate that our controls showed typical rCBF changes. This is particularly important because we studied a relatively small number of healthy normotensive controls. Although few have studied middle-aged individuals screened for hypertension, we can compare the present results to findings for two age-appropriate groups examined with the same tasks in our PET facility, as well as to a number of other studies using comparable tasks but in younger college-age volunteers. Carter et al (unpublished observations, 1997) used the CPT and CPTskip to study schizophrenics with the same PET techniques that we used. The control group for this study had
a mean age of 39 years. CPT performance in the control subjects was associated with prefrontal and frontal activation (Brodman’s areas 44 and 46) that was predominantly lateralized to the right hemisphere, as well as a bilateral parietal (Brodman’s area 40) activation. Becker et al., with a similar PET technique, used the verbal episodic memory task to study patients with Alzheimer’s disease and had a normal control group with a mean age of 66 years. They compared eight-word and three-word free recall tasks and observed bilateral frontal activation differences in their control group, but the area showing differences for the eight- and three-word recall was larger in the right hemisphere. Parietal activation was not observed in their study. Thus, the two comparable studies from the Pittsburgh laboratory generally support the right prefrontal/frontal activation observed in the present study, but they did not find the parietal involvement that we observed.

Cabeza and Nyberg10 recently reviewed all PET studies of cognition with normal predominantly young adult subjects. They reported six comparisons in the literature between a control and a sustained attention condition, comparable to our CPTs. In agreement with our findings, four of these comparisons showed right frontal activation and three of them right parietal activation. There were no reports of left frontal activation and only one of left parietal activation. Cabeza and Nyberg also reported on two comparisons of verbal episodic memory with a control task. Of these 12 studies, eight reported right frontal activation, one reported left frontal activation, and the remainder of the activations were bilateral. Our finding of predominantly right parietal change in control subjects is not, however, consistent with the literature reviewed; there was only one report of right parietal activation and two reports of left parietal activation, with the clear majority of comparisons showing bilateral activation. Cabeza and Nyberg’s review10 also suggested that working memory (involved in our CPTsk) evoked primarily bilateral frontal and parietal activations. Other reviews1,11,12 draw similar conclusions to those of Cabeza and Nyberg. Overall, the evidence suggests that our control subjects showed rCBF activations that were consistent with the majority of prior investigations of sustained attention and verbal episodic memory; our evidence for right frontal/prefrontal activation is very consistent with previous reports, as is parietal activation, but right lateralized parietal activation has not been widely observed.3,4,12–15

The failure of hypertensive subjects to demonstrate increased rCBF response with increasing task difficulty is significant given the representativeness of the rCBF task responses in our control subjects. We cannot claim that we have demonstrated a failure of neural activation or even metabolic activation in response to these tasks. Fox et al.10 suggested that brain activation differentially alters brain glucose uptake, oxygen metabolism, and blood flow. This suggestion remains controversial,17,18 but it prevents definitive interpretation of blood flow changes in terms of metabolic or neural activation. Furthermore, hypertension may alter vascular anatomy or metabolism such that the relationship is altered between blood flow and neural activation. For example, hypertension may change the permeability of the vascular wall to vasoregulatory compounds and thus alter the responsiveness of the vasculature to metabolic needs of the neural tissue. Further work will be needed to determine whether rCBF changes in hypertension represent a change in neural activation of the areas examined.19 Our working hypothesis is, however, that hypertension alters the responsiveness of the cerebrovasculature to neural activation. Responsiveness may decline because of chronic arteriolar vasoconstriction and reduced distensibility of nutritive vessels resulting from the hemodynamic adjustment of the brain to systemic hypertension.20–24 In our results, control subjects showed greater relative rCBF than hypertensive patients only during task processing but not during a resting visual-fixation condition.

Hypertensive patients showed rCBF responses to the CPT and verbal recall tasks that were in many instances lateralized to left hemisphere areas. The predominantly left frontal and prefrontal changes in rCBF during the tasks differed from the right lateralized changes in both our controls and in the literature just reviewed. Activation of functionally homologous areas in the left hemisphere may compensate for the inability to further activate right hemisphere areas among hypertensives. Quantitative rCBF measurements will be required, however, to test our working hypothesis that hypertensives show relatively enhanced nutritive CBF during rest and to assess the reasonableness of our compensation argument. Others have suggested that compensatory activation of regions occurs with added task difficulty because of either task requirement or physiological impairment. Smith et al.13 reported the recruitment of lateralized homologous structures with increasing difficulty of short-term memory tasks. Becker et al.4 have made similar suggestions for Alzheimer’s disease patients. With the present data, we can suggest such compensation but not prove that the enhanced left hemisphere rCBF response of hypertensives is in fact compensatory. The demonstration of compensation would be difficult; ideally, measurements should be available for the same individuals before the establishment of hypertension, during a hypertensive phase, and after reversal of the hypertension. Such data would permit a separation of strictly hemodynamic effects on rCBF responses from effects of other consequences of essential hypertension.

Our results raise a number of general issues about the interpretation of PET results in patients with vascular disease but also suggest that PET results may be useful in showing cerebrovascular and cognitive sequelae of hypertension. More work will be required to verify and extend the present results. Such work should define the relative role of neural/vascular changes correlated with hypertension, further exploring such factors as the degree of extracranial and intracranial atherosclerosis and the role of small white matter lesions.22,23 Our findings provide an impetus for the further examination of these issues and may elucidate earlier studies that demonstrated neuropsychological deficits in hypertensive compared with normotensive subjects.25–27

Acknowledgment
The support of National Institutes of Health grants HL57529 and HL40962 is gratefully acknowledged.
References

Cerebral Blood Flow in Hypertensive Patients: An Initial Report of Reduced and Compensatory Blood Flow Responses During Performance of Two Cognitive Tasks
J. Richard Jennings, Matthew F. Muldoon, Christopher M. Ryan, Mark A. Mintun, Carolyn C. Meltzer, David W. Townsend, Kim Sutton-Tyrrell, Alvin P. Shapiro and Stephen B. Manuck

Hypertension. 1998;31:1216-1222
doi: 10.1161/01.HYP.31.6.1216

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/31/6/1216

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/