Reduction of Functional Neuronal Connectivity in Long-term Treated Hypertension

Marc J. Mentis, Judith Salerno, Barry Horwitz, Cheryl Grady, Mark B. Schapiro, Declan G.M. Murphy, Stanley I. Rapoport

Background and Purpose Anatomic imaging of patients with chronic well-treated hypertension has demonstrated dilatation of the lateral cerebral ventricles and left brain atrophy, whereas positron emission tomography has shown only subtle reductions in regional cerebral metabolic rates for glucose in some subcortical nuclei. To further explore the implications of the imaging changes, an analytic technique designed to determine functional neuronal connectivity between regions of interest (ROIs) was applied to the data on regional cerebral metabolic rates for glucose to determine if and where in the brain reduction of functional neuronal connectivity occurred.

Methods Glucose metabolism was measured by positron emission tomography in 17 older men (age, 68±8 years) with well-controlled, uncomplicated hypertension of at least 10 years' duration and in 25 age- and sex-matched healthy control subjects. A significant correlation difference analysis was performed to determine which ROI pairs had reduced correlation coefficients (reduced functional neuronal connectivity). The vascular pattern of the reduction was determined after allocating the ROIs to their appropriate vascular territories.

Results Compared with the control subjects, hypertensive patients had reduced correlation coefficients in cortical territories of the internal carotid artery but not of the vertebral arteries. The border zone supplied by the middle and anterior cerebral arteries was most affected.

Conclusions The border zone between the anterior and middle cerebral arteries is vulnerable to ischemia from carotid pathology, systemic hypotension, or both. We hypothesize that although these hypertensive patients were "well controlled" and had normal neuropsychological tests, they may have experienced ischemia severe enough to cause border zone reduction of functional neuronal connectivity as a result of carotid pathology, antihypertensive medications, hypotensive episodes with a right-shifted autoregulation curve, or other factors in isolation or combination.

Key Words • carotid arteries • cerebral blood flow • glucose • hypertension • tomography, emission-computed

Quantitative magnetic resonance imaging (MRI) of the brain has demonstrated significant lateral cerebral ventricle dilatation (31.5 mL for both lateral ventricles compared with 18.4 mL in control subjects) and significant left cerebral hemisphere atrophy in patients with at least 10 years of treated hypertension who had no measurable cognitive deficits or other evidence of end-organ involvement.1 These studies extended a computer-assisted tomographic (CT) demonstration of ventricular dilatation in hypertensive patients with complications that included focal neurological signs and left ventricular hypertrophy.2

Salerno et al3 recently used positron emission tomography (PET) to examine global and regional cerebral metabolic rates for glucose (CMR$_{\text{glc}}$ and rCMR$_{\text{glc}}$) in the hypertensive group that evidenced dilatation of the lateral cerebral ventricles and cortical atrophy (see above).1 These PET results suggested that the effect of well-treated chronic hypertension on brain glucose metabolism is minimal, perhaps with relevant reductions (on the order of -10%) in subcortical nuclei.

To further explore the implications of brain atrophy, ventricular dilatation, and minimal mean rCMR$_{\text{glc}}$ abnormals in the same hypertensive group, we decided to use an analytic technique4 that uses rCMR$_{\text{glc}}$ data to evaluate functional neuronal connectivity between region of interest (ROI) pairs. This technique, which uses a correlation approach, extracts information about the relation between ROIs rather than comparing isolated ROI values. The fundamental premise is that if ROI A and ROI B are functionally related (by direct or indirect neuronal connections), their metabolic rates across all subjects will be highly correlated, ie, their correlation coefficient will be large. When there is no functional relation between the two regions, there will be no relation between their metabolic rates, and their correlation coefficient will be small. The size of the correlation coefficient is believed to be a measure of the strength of the functional neuronal connectivity between the two regions. By comparing the difference between the size of the correlation coefficients between two groups of subjects (significant correlation difference [SCD]), we can determine if one of the groups has reduced functional neuronal connectivity.4 In the past, we have been able to demonstrate functional neuronal connectivity reduction even when no significant difference between mean ROI values was detected.3-7

Because different hypertensive pathophysiological mechanisms cause cerebral damage in different vascular territories, our aim was to describe the vascular territorial pattern of any abnormalities we might find to provide data about the etiology or pathophysiology of the hypertensive changes. Therefore, we assigned the ROIs to their appropriate vascular territories and per-
formed two analyses on the data. We compared the mean absolute metabolic rate of each vascular territory between the two groups, and we applied the SCD analysis to the ROIs to determine if any vascular territory had a significant reduction of functional neuronal connectivity. An abstract of part of this work has been published.8

Subjects and Methods

Hypertensive Patients and Control Subjects

All participants were volunteers in an ongoing study of brain structure and function in hypertension at the Laboratory of Neurosciences of the National Institute on Aging; admission criteria have been presented in detail and are summarized here. Seventeen hypertensive men were studied (mean±SD age, 68.2±7.8 years; range, 51 to 80 years). Mean duration of hypertension was 15.4 years (range, 10 to 24 years). Available medical records showed good control of hypertension. Apart from hypertension, patients had no medical, surgical, or psychiatric problems; no evidence of end-organ damage; and no secondary causes of hypertension or disorders that might contribute to brain dysfunction as determined by history, physical examination, chest x-ray, electrocardiogram, MRI, and laboratory tests. Brain atrophy or white matter hyperintensities on MRI10,19 were not exclusionary criteria.

A 2-week medication washout period was implemented to avoid the influence of antihypertensive therapy on cognitive performance11 and to avoid the unknown, possibly confounding effects of different medication regimens on the PET scans. Ten patients were on a single-drug regimen (three receiving an angiotensin-converting enzyme inhibitor, two receiving β-blockers, one receiving a calcium channel blocker, and four receiving diuretics), and seven were receiving two drugs (a diuretic plus one of the above-mentioned drugs). Blood pressure was measured daily for patients off medication. During the washout period, no patient had sustained blood pressure elevations of more than 200 mm Hg systolic or 115 mm Hg diastolic. The control group consisted of 25 age-matched male volunteers (mean±SD age, 65.5±8.9 years; range, 52 to 83 years) with no medical, surgical, or psychiatric problems. Control subjects underwent the same neuropsychological tests and PET scans as did the hypertensive patients.

Hypertensive patients and control subjects were matched for all clinical criteria except blood pressure.12 Systolic and diastolic pressures were significantly higher in the hypertensive patients both on and off medications. There was no statistical difference between the groups with respect to age, mean scores for formal neuropsychological tests, handedness, or a battery of blood chemistries.

Positron Emission Tomography

Resting PET studies were performed with the tracer (18F)-2-fluoro-2-deoxy-D-glucose on a Scanditronix PC-1024-7B tomograph that can acquire data simultaneously from seven slices with an in-plane resolution of 6 mm and axial resolution of 10 mm. The methodology used to perform these resting scans has been described in detail.12

All scans were performed in the "resting state" with the participants' eyes patched and ears plugged and the lights dimmed. Arterial line placement allowed absolute rCMRglc to be calculated in units of milligrams of glucose per 100 g of brain per minute, using Brooks' modification13 of the operational equation of Sokoloff et al.1,2 with a lumped constant of 0.418.12 The set of scans for each subject consisted of 14 slices that were 6.9 mm apart and parallel to and ranging from 10 to 100 mm above the inferior orbital rim (IOM). The anatomy of the ROI template is well defined. With this template, the ROIs (on the template) were therefore situated within their appropriate vascular supplies. The average rCMRg value for each vascular territory was the average value of all the ROIs within the territory. The brain was divided into eight bilateral vascular territories (Fig 1); middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), MCA-ACA watershed, MCA-PCA watershed, cerebellar branches of the basilar artery, and perforating branches from the arteries at the base of the brain (origins or adjacent to the circle of Willis). None of the 65 ROIs were in the ACA-PCA watershed area.

Neuropsychological Tests

All subjects received the following tests: the full Wechsler Adult Intelligence Scale (WAIS)14, extended-range drawing test,20 block-tapping test,21 Whitehouse syntax comprehension test,20 controlled word association (or FAS) test,21 Trail Making Test parts A and B,20 and Porteus Maze Test.24 Statistical Analysis

Absolute rCMRg Analysis

The 65 ROIs were grouped into seven vascular territories (Table 1), forming a 2×7 (group by territory) repeated-measures design. This was analyzed as a multivariate analysis of variance to avoid assumptions of compound symmetry or sphericity, followed by a post-hoc Tukey test for unequal sample size to determine the effect of group on absolute rCMRg values for each vascular territory.

Correlation Analysis

The principles of and rationale for using the SCD analysis have been presented in the introduction. SCD analysis has been described in detail and validated elsewhere.1,2 How the SCD analysis was applied in the present study is described after the mathematics are briefly reviewed.

Pearson's correlation coefficients26 were calculated between ROI pairs separately for the hypertensive and control groups. Normalized (rCMRg/CMRg) rather than absolute metabolic rates were used because PET data intersubject differences are usually greater than ROI differences within a scan; the latter are the differences of interest. Normalizing the data removes the effect of intersubject variability while retaining within-scan ROI differences.

The correlation coefficients for each ROI pair were then compared between the two groups by calculating a Z statistic that allowed the significance level of the comparison to be determined. Correlation coefficient values (which are not normally distributed) needed to be converted to a normal distribution, using a Fisher Z transformation, for the Z statistic to be calculated.24 Because the sample size was relatively small, the standard error of the correlation coefficients used in calculating the Z statistic could have been inordinately influenced by a few outliers; therefore, a "normal theory" as well as a "bootstrap"27 method was used in its estimation. For a between-group correlation coefficient difference to be considered an SCD, Z scores derived by both methods had to be significant at α<.05.

Application of SCD Analysis to the Present Study

The null hypothesis was that there were no SCDs between the hypertensive and control groups. Furthermore, if SCDs occurred by chance alone, there would be as many SCDs in which the hypertensive group had the smaller correlation coefficient of the pair as SCDs in which the hypertensive group had the larger.
<table>
<thead>
<tr>
<th>Brain Region of Interest*</th>
<th>Vascular Territories</th>
<th>Control Subjects, mg/100 g/min (n=25)†</th>
<th>Hypertensive Patients, mg/100 g/min (n=17)†</th>
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<tr>
<td>Right premotor (1-3)</td>
<td>Carotid</td>
<td>8.68±1.28</td>
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<td>Left Insula (18)</td>
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<td>Left anterior medial temporal (34)</td>
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<td>Right inferior temporal (55)</td>
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<td>Left inferior temporal (56)</td>
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<td>Right caudate nucleus (57)</td>
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<td>Right lentiform nucleus (58)</td>
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<td>Left lentiform nucleus (61)</td>
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<td>Right thalamus (59)</td>
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<td>Left thalamus (62)</td>
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<td>Left cerebellum (64)</td>
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<td>Vermis (65)</td>
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<tr>
<td>Brain</td>
<td>MCA/ACA/Percutaneousartery branches from the arteries at the base of the brain; and CERE, cerebellar branches off the basilar artery.</td>
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</table>

*MCA indicates middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PERF, perforating branches from the arteries at the base of the brain; and CERE, cerebellar branches off the basilar artery.

*Numbers in parentheses indicate region of interest number used on X and Y axes in Fig 3.

†Values are mean±SD for each vascular area.

‡P<.001 (see Fig 2).
The numbers of SCDs were counted in each vascular territory, and "splits" were determined. A split was defined as the ratio between the number of SCDs in which the hypertensive group had the lower correlation value of the pair to the number of SCDs in which they had a higher value. If splits differed significantly from a 50%/50% distribution (using a χ² test expecting equal proportions), the SCDs in the territory were considered not to have occurred by chance. Thus, if a vascular territory had 100 SCDs made up of 70 in which the hypertensive group had the smaller correlation in the pair and 30 in which the hypertensive group had the larger, a χ² test would be used to determine if this 70/30 split was significantly different from the 50/50 split expected by chance. Significantly more small correlation coefficients would be interpreted as a reduction of functional neuronal connectivity in the region.

**Results**

**Absolute rCMR_{glc} by Vascular Territory**

Table 1 lists mean absolute rCMR_{glc} by vascular territory for the control subjects and hypertensive patients and identifies the ROIs that contributed to each territory. The interaction of rCMR_{glc} and group was statistically significant (P<.05) (Fig 2). Tukey's honestly significantly different post-hoc test (for unequal sample size) demonstrated that only the territory supplied by perforator arteries from the circle of Willis and initial segments of the cerebral arteries had a significantly lower rCMR_{glc} in the hypertensive group than in the control group (P<.001) (Fig 2).

**ROI Correlation Coefficients by Vascular Territory**

The analysis of 65 ROIs resulted in a total of 2080 pairwise correlations that were calculated for each of the groups. Of these correlations, 1167 (56.1%) were smaller and 913 (43.9%) were larger in the hypertensive patients (χ²=31.02, P=.0001). Of the 2080 correlation differences that were calculated between hypertensive patients and control subjects, 109 were statistically significant (SCDs) by both the normal and bootstrap methods at α=.05 (when each difference was considered individually). Of these 109 differences, 73 (67%)
were smaller and 36 (33%) were larger in the hypertensive patients, a distribution that was not expected by chance ($\chi^2=14.2, P=.0002$).

Fig 3 illustrates the matrix of SCDs arranged by vascular territory, and Table 2 lists the number of significant differences in each vascular territory and the likelihood of the pattern occurring by chance. Numbers on the X and Y axes of Fig 3 correspond to those listed next to the names of the regions in Table 1 to identify specific ROIs.

In the internal carotid territory, there were 95 SCDs of 1827 correlations, with a significant 73/22 split ($\chi^2=27.4, P=.0001$). The territory supplied by the basilar artery had 53 SCDs of 855 correlations, with a nonsignificant 23/30 split ($\chi^2=.93, P=.34$). To minimize overlap between the territories, SCDs between each of these areas and the MCA-PCA watershed were not counted.

The internal carotid territory was subdivided into MCA, ACA, and MCA-ACA watershed territories. In the MCA territory, of a total of 944 correlations, there were 55 SCDs with a significant 39/16 split ($\chi^2=9.62, P=.002$). The ACA had 19 SCDs of a total of 350 correlations, with a significant 16/3 split ($\chi^2=8.90, P=.003$). The MCA-ACA watershed had 51 SCDs of a total of 999 correlations, with a significant 47/4 split ($\chi^2=36.26, P=.0001$).

There was no significant split between hypertensive patients and control subjects in the pattern of SCDs in the basilar territory as a whole (see above) or in its posterior cerebral or cerebellar subdivision. The MCA-PCA watershed territory, which receives blood from the internal carotid and basilar arteries, had only 4 SCDs of 123 correlations. The subcortical forebrain nuclei, which are supplied by perforators from arteries at the base of the brain, had 369 correlations, of which only 19 were SCDs, with a nonsignificant 12/7 split ($\chi^2=1.32, P=.25$). When the thalamic nuclei alone were evaluated, of a total of 124 correlations, 14 were SCDs, with a significant 11/3 split ($\chi^2=4.57, P=.03$).

**Discussion**

In the SCD analysis, which was designed to look at the metabolic relation between ROIs, we demonstrated that the hypertensive group had smaller correlation coefficients (reduction of functional neuronal connectivity) significantly more frequently in cortical territories of the MCA (39/16 split, $P=.002$) and of the ACA (16/3 split, $P=.003$) and particularly in the MCA-ACA watershed area (47/4 split, $P=.0001$). A similar reduction was demonstrated between the thalamus and other brain regions (11/3 split, $P=.03$). There were no between-group differences in the size of correlation coefficients in the brain supplied by the basilar artery (posterior
cerebral and cerebellar branches), the border zone between the MCA and PCA, or the perforator territory (if all nuclei were considered together).

The means comparison of vascular territory metabolic rates confirmed the earlier PET findings of minimal differences between the two groups, with the perforator territory alone having a significantly lower glucose metabolic rate in the hypertensive group. In the corresponding analysis by Salerno et al (Salerno JA, Mentis MJ, Gonzalez-Aviles A, Grady C, Wagner E, Schapiro MB, Rapoport SI. Unpublished data), the thalamic and lenticular nuclei showed significant bilateral reductions in rCMR<sub>gl</sub>, on the order of 10% in the hypertensive patients compared with control subjects, whereas the caudate nucleus showed no difference.

The patients in the present study were healthy apart from uncomplicated hypertension and received normal scores on a wide range of neuropsychological tests, which raises the question of the importance of the results. In a longitudinal study using <sup>133</sup>Xe inhalation, neurologically normal subjects with hypertension and other risk factors for cerebrovascular disease had marked reductions in regional cerebral blood flow (rCBF) for as long as 2 years before developing focal signs. Yao et al showed that two nondemented hypertensive subjects with leukoaraiosis, who had measurably reduced rCBF and increased oxygen extraction fraction (OEF) on PET, later developed dementia. The reduced rCMR<sub>gl</sub> in the basal ganglia (perforator artery territory) of our hypertensive patients may therefore represent a preclinical expression of the vascular changes, ischemia, lacunar infarcts, hemorrhages, or leukoaraiosis that commonly occurs in this area in hypertensive patients.

The smaller correlation coefficients (reduction of functional neuronal connectivity) found only in the internal carotid artery territory, and sparing the basilar, might reflect early effects of hypertensive vascular pathology (lipohyalinosis, medial hypertrophy, and atherosclerosis) despite good control of hypertension. This vascular pathology is statistically more severe in the carotid and its branches than in the basilar or vertebral circulation. The surprising finding was that the territory with the greatest fraction of significantly reduced correlation coefficients was the border zone between the MCA and ACA. This was unexpected because the etiologies associated with damage to this area are extracerebral, usually carotid pathology, systemic hypertension, or both, rather than intracerebral vascular changes. Our ability to grade the severity of our patients' carotid pathology was limited because we did not include carotid Doppler studies in our assessment. However, none of our patients had a carotid bruit, which in asymptomatic subjects does not reduce the risk of subsequent stroke. The other etiological possibility is that hypotensive episodes, perhaps in combination with carotid atherosclerosis, were responsible for this border zone reduction of functional neuronal connectivity even though the group was believed to be compliant with medication and "well controlled."

Autoregulation of CBF reflects the ability of the brain to maintain a constant blood flow despite changes in perfusion pressure by cerebral arteriolar constriction when perfusion pressure falls and by arteriolar dilatation when it rises. The lower limit of autoregulation is the perfusion pressure below which maximal vasodilation becomes inadequate, resulting in CBF decrease and compensatory increase in OEF. Brain ischemia occurs when maximal compensatory OEF is exceeded.

In hypertensive patients, the blood pressure range over which autoregulation maintains a constant CBF (plateau) is shifted to the right, to higher arterial pressures. Nevertheless, autoregulation may not be sufficient to maintain normal CBF, resulting in increased OEF, as was described initially with the Kety-Schmidt technique and more recently in PET studies of hypertensive patients with focal neurological signs and leukoaraiosis. Increased OEF, in controlled hypertension, suggests that blood flow and oxygen demand are operating at the lower limit of autoregulation, making the brain, and especially the border zones, vulnerable to minor hypotensive episodes.

Additional factors may contribute to such vulnerability. By definition, successful antihypertensive therapy effectively reduces mean blood pressure. In many patients, blood pressure control is accompanied by a return of the autoregulatory plateau to the normal pressure range, but in some (possibly those with longstanding hypertension and irreversible vascular changes) a return does not occur and the lower limit may be quite close to medically induced mean systemic pressure. The average age of our hypertensive patients was 68 years, and it is known that elderly persons may be particularly vulnerable to postural and postprandial hypotensive episodes. Hypertensive patients may have wider ranges of acute changes in systemic blood pressure than nonhypertensive individuals, thereby exposing their brains to longer periods of ischemia during similar hypotensive episodes. Some antihypertensive medications may cause hypovolemia, increase blood viscosity, block autonomic responsiveness, or decrease CBF.

Hypertensive autoregulatory changes taken together with factors of carotid pathology, drug treatment, age, irreversibility of intracerebral vascular pathology, and the vicissitudes of daily living might have led to accumulated hypertensive ischemia insufficient for infarction but sufficient to irreversibly interrupt normal neuronal connectivity in the border zone between the MCA and ACA in our "well-controlled" older patients with hypertension of more than 10 years' duration. This highlights the limitations of current antihypertensive management. Clearly, therapy should be designed not only to control systemic blood pressure but also to ensure sufficient autoregulation to prevent increased OEF so as to maintain a range of constant flow matched to the controlled blood pressure. In any case, follow-up studies are required to determine whether the changes that we have identified are early stages of vascular dementia or stroke; if so, judicious use of drugs could slow down the progression of the disease. In the 3 years after initial PET studies, one of our hypertensive patients had an intracranial hemorrhage, one underwent four-vessel coronary artery bypass grafting, and one had a silent anterior wall myocardial infarction. None have become demented or died.

**Acknowledgments**

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