Patterns Of Cerebral Hypoperfusion Compared Among Demented and Nondemented Patients With Stroke

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Background and Purpose: No reports are available that compare local cerebral perfusion among groups of patients suffering from multiple cerebral infarctions with and without cognitive impairments. The present study was designed to correlate changes in regional cerebral perfusion that may lead to dementia among patients with multiple cerebral infarctions by comparing measurements of local cerebral blood flow.

Methods: Local perfusion was measured using xenon-contrasted computed tomographic scanning among two groups of patients who had suffered from multiple cerebral infarctions: Group D (n=12) were demented and had severe cognitive impairments, and group I (n=11) were cognitively intact. Results were compared with similar measurements among neurologically and cognitively normal, age-matched volunteers (group N, n = 16).

Results: Mean local perfusion values were reduced among both groups with cerebral infarctions but to a more marked degree in group D (p<0.05). Perfusion of cerebral white matter was diffusely and severely reduced in group D (p<0.05) but was mildly reduced only in frontal and capsular white matter in group I (p<0.05). Perfusion of cerebral cortex was reduced in frontal (p<0.01) and temporal (p<0.01) regions among both groups but to a significantly greater degree in group D subjects (frontal, p<0.05; temporal, p<0.01), who also showed hypoperfusion of the occipital cortex (p<0.05), apparently because of underlying leukoaraiosis and cortical disconnections. Perfusion of the basal ganglia was reduced to the same degree among both groups of stroke patients (p<0.01).

Conclusions: Leukoaraiosis with white matter hypoperfusion appears to be an important determinant for cognitive impairments among patients with multiple cerebral infarctions. (Stroke 1992;23:686-692)

KEY WORDS • dementia • white matter • cerebral infarction

Among the elderly in the United States and Europe, cerebrovascular disease is a frequent cause of dementia, second only to Alzheimer's disease, whereas in Asia cerebrovascular disease is the most common cause of dementia. In 1974 the term "multi-infarct dementia" was proposed to describe the most common form of vascular dementia by Hachinski and associates, who described an ischemic index that has proven useful for separating vascular dementia from Alzheimer's disease. The modified ischemic index was further modified by Loeb and Gandolfo to include evidence of cerebral infarctions detected by neuroimaging. The modified ischemic index now provides a high degree of diagnostic accuracy during life that is confirmed at autopsy.

Reports have consistently shown that local cerebral blood flow (CBF) and metabolism among patients with multi-infarct dementia decrease in a patchy manner and that these local CBF reductions correlate directly with cognitive impairments. However, regional hemodynamic mechanisms responsible for the stepwise declines in cognitive impairments that characterize patients with multi-infarct dementia have received little attention. As far as can be determined, no reports are available in which local cerebral perfusion has been compared among age-matched groups of patients suffering from multiple cerebral infarctions with and without cognitive impairments.

The present study was designed to correlate changes in regional cerebral perfusion, which may lead to dementia among patients with cerebral infarctions, by comparing measurements of local CBF among two groups of patients with multiple strokes followed in this laboratory for several years. One group had cognitive impairments and the other did not.

Subjects and Methods

Subjects studied included 16 neurologically normal age-matched volunteers in group N (n=16 [six men, 10
women; age, 67±10 years [range, 57–86 years]), all of whom had normal Cognitive Capacity Screening Examination (CCSE) scores (29±2; range, 27–31), and two groups of patients with multiple cerebral infarctions, one with and the other without cognitive impairments. The demented group D (n=12 [seven men, five women]; age, 72±9 years [range, 54–83 years]) showed statistically (p<0.01) severe cognitive impairments (CCSE scores, 17±6) compared with the intact group I (n=11 [eight men, three women]; age, 66±8 years [range, 51–72 years]), whose cognitive test scores were in the normal range. Furthermore, as illustrated in Figure 1, group D and group I have been followed longitudinally for approximately 5 years so that serial neurological examinations and cognitive testing could be performed. The normal volunteers have been followed for 5.7±0.8 years; group D has been followed for 4.6±1.5 years and group I for 5.4±0.6 years.

All patients and volunteers have undergone the following diagnostic assessments: history; medical and neurological examinations; CCSE scoring, as well as other neuropsychological test batteries to establish the presence or absence of cognitive impairments; and grading according to Hachinski’s ischemic index and according to relevant clinical and laboratory tests to determine the presence or absence of stroke and risk factors for stroke. Patients in group D met criteria for the diagnosis of dementia according to recommendations listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) of the American Psychiatric Association. Cognitive Capacity Test scores of <25 have been shown to correlate well with other neuropsychological and cognitive test scores performed among the elderly (including the Wechsler Adult Intelligence Scale and the Mini-Mental Status Questionnaire) and provide a reliable index for following the course of patients with dementia.14-16

Educational achievements by all subjects were at the high school graduate level or higher. All stroke patients had multiple low-density areas confirmed by computed tomography (CT) and high-density areas by T1 magnetic resonance imaging (MRI), which were considered compatible with the diagnosis of multiple cerebral infarctions. Associated risk factors for stroke, including hypertension, heart disease, hyperlipidemia, diabetes mellitus, and smoking, showed no differences among both stroke groups. Identification of the type of strokes for each patient was made according to recommendations listed by the Classification of Cerebrovascular Disease III of the National Institute of Neurological Disorders and Stroke.17 As shown in Table 1, all patients were classified as suffering from lacunar strokes, and five patients (41.7%) in group D and six patients (54.5%) in group I also had occlusion of one internal carotid artery. Occlusion of the internal carotid arteries was considered to be present when Doppler or angiographic examinations were reported to disclose occlusion within the internal carotid arterial system. There were no significant differences in the type of strokes among the two groups.

Local CBF was measured by serial CT scanning during inhalation of 27% stable xenon gas used as the contrast agent. The time course of arrival of the radiopaque gas through the different cerebral volumes of interest was determined by using densitometric changes of local Hounsfield numbers (Xe-CT CBF method).18 Patients and volunteers fasted for 4 hours before each CBF measurement. Participants reclined on a CT table while inhaling 100% oxygen for 2–4 minutes before xenon inhalation. One or two CT levels were selected to include frontal, temporal, parietal, and occipital cortex, caudate nucleus, putamen, and thalamus at 10 and 20 mm above the orbitomeatal line. After two noncontrast control CT scans, seven serial CT scans were obtained at 1-minute intervals between the second and eighth minute of inhalation of 27% xenon gas using one of two high-resolution CT scanners (Somatom DR Version H, Siemens Medical Systems, Inc., Iselin, NJ. or Picker Syneview SX 1200, Picker International, Inc., Cleveland, Ohio). The CT scanning parameters were 96 kV (peak), 540 mA, 8-mm slice thickness at one level with a 5-second scanning time for Somatom DR-H, and 130 kV (peak), 140 mA, 10-mm slice thickness at two levels back-to-back with a 2-second scanning time for the Picker Syneview. End-tidal partial pressures for xenon gas and carbon dioxide were recorded on a polygraph.

Local CBF values were generated as color-coded images superimposed directly on each CT slice programmed by means of a desktop computer. Two control scans were used as baseline, and seven serial postenhancement scans were used to define multiple local tissue saturation curves for each slice according to Kety’s formula. The original CT images (512×512 pixels) were compressed to 128×128 pixels before calculating local CBF values, with precalculation and postcalculation smoothing (3×3). By identifying specific anatomic locations for gray and white matter on the plain CT images with the cursor, local CBF values for 11 representative regions for each hemisphere (a total of 22 regions including frontal, temporal, parietal, and occipital cortex, caudate nucleus, putamen, thalamus, frontal, parietal, occipital, and capsular white matter) were automatically computed. The CT scanning level

FIGURE 1. Graph showing Cognitive Capacity Screening Examination (CCSE) scores plotted against time among multiple cerebral infarction patients with dementia (group D; n=12, ●) and without dementia (group I; n=11, ○). Group D patients had fluctuating CCSE scores over time that were consistently <25 throughout the follow-up interval (4.6±1.5 years), but group I patients had CCSE scores that consistently fell within normal limits (5.4±0.6 years).
Table 1. Locations of Lacunar Infarctions by Computed Tomographic Scanning, Volume Ratios of Infarcted Brain to Total Brain Volume, and Stroke Type Among Patients With and Without Cognitive Impairments

<table>
<thead>
<tr>
<th>Group and patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Lacunar infarction location</th>
<th>Volume ratio (%)</th>
<th>Etiology</th>
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<tr>
<td>Group D</td>
<td></td>
<td></td>
<td>FC</td>
<td>TC</td>
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<tr>
<td>1</td>
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<td>75</td>
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FC, frontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; CAU, caudate nucleus; PUT, putamen; THA, thalamus; FW, frontal white matter; PW, parietal white matter; OW, occipital white matter; INT, internal capsule; Volume ratio, ratio of volume of infarcted brain to total brain volume; Etiology, etiologic classification of strokes; Group D, demented patients with cognitive impairments; Group I, cognitively intact patients; M, male; F, female; L, lacunar strokes; ICAO, occlusion of internal carotid artery.

and regions of interest were standardized between patients. The levels of slices selected for the CT CBF measurements were fine-tuned so that the slices were comparable for anatomic structures imaged from patient to patient. The size of the volumes each pixel represents, expressed as voxels, and their anatomic location were the same for each patient.

The electroencephalogram and electrocardiogram were monitored throughout CBF measurements. Patients and volunteers signed informed consent before each CBF measurement. The protocol for these studies has been approved annually by the Institutional Review Board of the Veterans Affairs Medical Center, Houston, Tex. Xenon-CT CBF measurements were performed 2.3±1.5 years after the last stroke for group I patients and 2.5±1.9 years after the last stroke (associated with cognitive impairments) for group D patients.

Ratios of the volume of infarcted or atrophic brain to total brain volume were measured from the plain CT scans among both groups of patients with multiple cerebral infarcts according to methods described previously.16 Volumes of infarcted brain were expressed as percentage ratios of the area that had Hounsfield numbers of <25, which is the threshold density for infarcted brain, to total volume of brain measured at each level. Total volume of brain tissue is defined as the intracranial volume excluding the ventricular systems and subarachnoid space.

The volumes of leukoaraiosis were quantified for each patient using computerized densitometric measurements for reduced Hounsfield units in white matter and then compared among the three groups. Details of the densitometric method have been reported previously.19 In brief, threshold values for abnormal Hounsfield unit numbers in volumes of white matter (indicating volumes of leukoaraiosis) were set between 25 and 34. Regions of cortical atrophy that fell within these values because of partial volume effects of CT imaging (±0.1% of total volume of brain tissue) were excluded from analysis by cursoring. Volumes for each compartment were then expressed as percentage ratios to total volume of brain tissue measured at each CT level. Standard deviations for Hounsfield numbers were ±0.2 when a standard CT phantom was scanned rapidly 11 times, indicating excellent densitometric reproducibility for both CT scanners.18

The validity of CT densitometry had been confirmed by previous comparisons of MRI with CT imaging among patients with either multi-infarct dementia or senile dementia of the Alzheimer's type. Magnetic resonance imaging is more sensitive for identifying white matter lesions by T2-weighted scans,20 but when
CT evidence of leukoaraiosis was identified, it was invariably confirmed by MRI imaging. Analysis of 25 patients with multi-infarct dementia, which included patients in the present study, revealed that the presence of diffuse periventricular high-intensity lesions in white matter (leukoaraiosis) detected by MRI and CT is one of several discriminant factors that assist in the differentiation of multi-infarct dementia from senile dementia of the Alzheimer’s type by neuroimaging. Magnetic resonance imaging was performed in three patients in group D and three patients in group I. The pattern and extent of leukoaraiosis were consistent with our CT findings of leukoaraiosis.

All data are presented as mean±SD. Statistical analysis was performed using Student’s t test unless otherwise stated.

Results

Figure 1 compares CCSE scores plotted against time among patients with multiple cerebral infarctions associated with cognitive deficits (group D) and among patients with cerebral infarctions but without cognitive deficits (group I). Patients in group D exhibited CCSE scores that fluctuated but consistently fell to <25 throughout follow-up intervals, while group I patients exhibited CCSE scores that regularly tested within normal limits. It is apparent that there are fluctuations in cognitive test performance over time among patients with multi-infarct dementia, without the progressive downhill deteriorations that are characteristic of patients with Alzheimer’s disease. This lends internal validity to one important criterion (fluctuating clinical course) described as part of the scoring system of the Hachinski Ischemic Index.4

As shown in Table 1, locations of cerebral infarcts did not differ significantly between demented and non-demented stroke patients, nor did volumes of infarcted brain.18

Figure 2 displays results of comparisons using the Bonferroni test between pooled mean values for cortical, subcortical, and white matter perfusion among age-matched normal volunteers and the two groups of patients with cerebral infarctions. Compared with normals, global CBF values were reduced overall among both stroke groups (group D, 31.5±5.2 ml/100 g brain/min; group I, 36.3±4.9 ml/100 g/min, p<0.01), but reductions were more marked in group D (p<0.05). Cortical gray and white matter perfusions were also more reduced in group D (cortical gray, 35.3±6.0 ml/100 g/min; white matter, 15.9±1.8 ml/100 g/min) compared with group I (cortical gray, 44.7±7.6 ml/100 g/min; white matter, 19.0±2.5 ml/100 g/min), but subcortical gray matter perfusions were equally reduced among both stroke groups (group D, 42.3±7.7 ml/100 g/min; group I, 45.1±8.7 ml/100 g/min).

Figure 3 summarizes results of multiple comparisons using the Bonferroni test of mean perfusion values for 11 representative cerebral regions among normal volunteers and compared among the two groups of stroke patients with and without dementia. White matter perfusion values were diffusely and severely reduced in group D. However, in group I, white matter flow values were only mildly reduced and these reductions were limited to frontal (17.6±2.8 ml/100 g/min) and capsular white matter (20.3±4.8 ml/100 g/min). Perfusion values for frontal (group D, 35.6±7.3 ml/100 g/min; group I, 44.0±5.8 ml/100 g/min) and temporal cortex (group D, 34.9±6.4 ml/100 g/min; group I, 45.9±8.9 ml/100 g/min) were reduced among both groups of stroke patients but to a more marked degree in group D patients, who also

![Graph showing mean local cerebral blood flow (LCBF) values for cortical gray, subcortical gray, and subcortical white matter compared between age-matched normal volunteers and two groups of stroke patients with (group D) and without (group I) dementia.](image)
showed reductions in occipital cortical perfusion (35.5±7.4 ml/100 g/min).

Figure 4 displays typical maps of cerebral perfusion recorded from two representative patients with multiple strokes, one with and the other without cognitive impairments. Local CBF values for both patients were decreased in frontal, temporal, and subcortical gray matter and frontal white matter. However, reductions of cerebral perfusion are greater in the patient with cognitive impairments, particularly in white matter where local CBF reductions are more severe and diffuse.

Table 2 displays pooled ratios of volume of leukoaraiosis to total brain volume among elderly normal volunteers compared with the two stroke groups. The extent of leukoaraiosis among the demented patients far exceeded that among stroke patients who were cognitively intact; however, leukoaraiosis was more marked in both stroke groups compared with elderly normal volunteers. During CT CBF measurements, mean values for endtidal partial pressure for carbon dioxide did not differ

Table 2. Ratios of Volumes of Leukoaraiosis to Total Brain Volume Compared Among Patients With and Without Cognitive Impairments and Age-Matched Normal Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases (No.)</th>
<th>Ratio of leukoaraiosis to total brain volume (%)</th>
</tr>
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<tbody>
<tr>
<td>Group D</td>
<td>12</td>
<td>16.4±3.2**†</td>
</tr>
<tr>
<td>Group I</td>
<td>11</td>
<td>9.3±3.6‡</td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
<td>4.4±2.0</td>
</tr>
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</table>

Values are mean±SD. Group D, demented patients with cognitive impairments; Group I, cognitively intact patients.
**p<0.01 compared with normal subjects; †p<0.01 compared with group I; ‡p<0.05 compared with normal subjects.

Table 3. Correlations Between Global Cerebral Blood Flow, Cognitive Capacity Screening Examination Scores, and Ratios of Volumes of Leukoaraiosis and Infarcted Brain to Total Brain Volumes

<table>
<thead>
<tr>
<th>CCSE scores</th>
<th>Ratios of leukoaraiosis to total brain volume (%)</th>
<th>Ratios of infarcted brain to total brain volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global CBF</td>
<td>0.43*</td>
<td>−0.53*</td>
</tr>
</tbody>
</table>

CCSE, Cognitive Capacity Screening Examination; CBF, cerebral blood flow.
* p<0.05.
between groups (32.0±2.2 mm Hg among age-matched normal volunteers, 33.0±2.4 mm Hg for group D, and 31.4±2.0 mm Hg for group I). Mean arterial blood pressures also did not differ between groups (106±9, 110±14, and 104±7 mm Hg, respectively).

Table 3 shows correlations between global CBF, CCSE scores, and ratios of volumes of leukoaraiosis and infarcted brain to total brain volumes. Global CBF significantly (p<0.05) and directly correlates with CCSE scores and indirectly with ratios of volumes of leukoaraiosis at the time of the CT CBF measurements. However, correlations were not found between global CBF and volumes of cerebral infarction.

Discussion

Our study showed that cognitively impaired stroke patients have more severe and diffuse leukoaraiosis associated with reductions of white matter perfusion than do stroke patients who remain cognitively intact. Differences between the two stroke groups were particularly marked for white matter abnormalities in both frontotemporal regions, in which hypoperfusion was striking among the demented patients, as illustrated by case D-10 in Figure 4.

Previous studies have correlated the location of cerebral infarctions among stroke patients with their measured cognitive impairments. Dementia has been reported to be associated with bilateral thalamic infarctions, lesions involving the thalamus of the dominant hemisphere, and with infarctions involving both thalamic and cortical areas supplied by the middle cerebral arteries. In a study of 15 patients with multi-infarct dementia designed to correlate local CBF reductions with cognitive test scores, positive correlations were reported between cognitive impairments and bilateral hypoperfusion of the frontotemporal cortex and thalamus. In these earlier studies, no attempts were made to correlate reductions of white matter perfusion with cognitive deficits, nor were control correlations made between stroke patients with and without cognitive impairments. Present results contrasting demented and nondemented stroke patients suggest that diffuse reductions of white matter perfusion are another important determinant of cognitive impairments.

Whether hypoperfusion of white matter associated with leukoaraiosis is due to ischemia alone or, in addition, is secondary to decreased metabolic demands of white matter resulting from disconnections between white and gray matter cannot be determined from the present studies. However, the observation that diffuse reductions of cortical flow are not consistent with the location of lacunar infarctions identified by CT and MRI scanning among demented patients suggests that cortical hypoperfusion is more likely to be due to functional deactivation rather than an indication of a primary role of ischemia.

Previous retrospective studies have attempted to correlate cognitive performance with semiquantitative estimates of leukoaraiosis determined by CT or MR imaging. These earlier studies showed that leukoaraiosis is occasionally present in asymptomatic elderly normal volunteers, but as the leukoaraiosis becomes more extensive, the likelihood of it being associated with cognitive deficits increases. If the severity ap proached that seen in the “Binswanger type” of advanced leukoencephalopathy caused by arteriosclerotic, amyloid, or sclerosing subcortical vasculopathy, the presence of dementia may be assured.

Leukoaraiosis was originally defined by Hachinski and associates as “abnormal regions of white matter disclosed by CT or MRI imaging.” Since then, a number of studies have implicated leukoaraiosis with advancing age, risk factors for stroke, focal neurological signs, cognitive impairments, dementia, and cerebral hypoperfusion. In a study of 15 patients with multi-infarct dementia designed to correlate local CBF reductions with cognitive test scores, positive correlations were reported between cognitive impairments and bilateral hypoperfusion of the frontotemporal cortex and thalamus. These conclusions were based on PET measurements showing that prominent hypoperfusion, coupled with hypometabolism, was concurrently measured in the frontotemporal cortex overlying the most severe zones of leukoaraiosis. Neuropathological observations also provide morphological support to the ischemia/hypoperfusion hypothesis for leukoaraiosis.

Taken together, these facts support the view that cognitive impairments among patients with multiple cerebral infarctions are regularly associated with leukoaraiosis, which appears to be due to ischemia and hypoperfusion of white matter, causing and reflecting disconnections between thalamocortical projection systems.

Acknowledgments

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