ORIGINAL CONTRIBUTION

Effects of Subcortical Cerebral Infarction on Cortical Glucose Metabolism and Cognitive Function

Lawrence T. Kwan, BS; Bruce R. Reed, PhD; Jamie L. Eberling, PhD; Norbert Schuff, PhD; Jody Tanabe, MD; David Norman, MD; Michael W. Weiner, MD; William J. Jagust, MD

Background: The mechanism of dementia in subcortical cerebral infarction is incompletely understood.

Objective: To determine how cognitive function is related to cortical metabolism in patients with subcortical infarction and a continuum of cognitive impairment.

Methods: We used positron emission tomography (PET) and the glucose metabolic tracer fludeoxyglucose F 18 to study 8 patients with subcortical stroke and normal cognitive function (S-CN), 5 patients with subcortical stroke and cognitive impairment (S-CI) who did not have dementia, 8 patients with subcortical stroke and dementia (S-D), and 11 controls with no cognitive impairment or stroke. A subset of patients had absolute regional cerebral metabolic rate of glucose (CMRglc) determined, while in all subjects regional tracer uptake normalized to whole brain tracer uptake was calculated. PET data were analyzed by constructing volumes of interest using coregistered magnetic resonance imaging data and correcting the PET data for atrophy.

Results: Global CMRglc was significantly lower in the patients with S-D than in the control and S-CN groups, with S-CI rates intermediate to those of the S-D and S-CN groups. Absolute regional CMRs of glucose were similar in the S-D and S-CI groups and in the control and S-CN groups. The regional pattern, however, showed lower right frontal regional CMRglc ratios in all stroke groups compared with the controls. There were modest correlations between performance on the Mini-Mental State Examination and whole brain CMRglc when all 4 groups were included.

Conclusions: These results demonstrate that subcortical infarction produces global cerebral hypometabolism, which is related to the clinical status of the patients. In addition, specific frontal lobe hypometabolism also appears to be a feature of subcortical infarction. Taken together, both global and regional effects on cortical function mediate the production of clinical symptoms in patients with subcortical strokes.

Arch Neurol. 1999;56:809-814

From the Center for Functional Imaging, Lawrence Berkeley National Laboratory, Berkeley, Calif (Mr Kwan and Drs Reed, Eberling, and Jagust); Department of Veterans Affairs, Martinez, Calif (Drs Reed and Jagust); Department of Neurology, University of California, Davis (Mr Kwan and Drs Reed and Jagust); Departments of Veterans Affairs Medical Center, Magnetic Resonance Unit (Drs Schuff, Tanabe, and Weiner), Radiology (Drs Schuff, Tanabe, Norman, and Weiner), Psychiatry (Dr Weiner), and Neurology (Dr Weiner), University of California, San Francisco.

CEREBRAL infarction as a cause of dementia has been well established for many years. Tomlinson and colleagues[1] clearly differentiated dementia caused by cerebral infarction from Alzheimer disease (AD) and applied the term *arteriosclerotic dementia* to cases of dementia with extensive infarction and minimal AD-type change. Hachinski et al[2] refined the concept by noting that cerebral infarction, rather than chronic ischemia, was the defining characteristic of this syndrome that they termed *multi-infarct dementia*. Within the past several years, new clinical criteria for the diagnosis of vascular causes of dementia have been suggested,[3,4] and the term *ischemic vascular dementia* has been applied in a further attempt to delineate the different physiological causes of dementia due to cerebrovascular disease.

Despite these considerable advances in nosology, much uncertainty concerning the pathophysiology and clinical significance of vascular dementia persists. Estimates of the frequency of the disorder vary considerably,[5,6] and diagnostic confusion extends even to neuropathological circumstances in which cerebrovascular disease and AD pathology coexist.[7,8] These difficulties are related to problems with both clinical and pathological diagnosis and to the considerable heterogeneity of vascular dementia.[9]

For editorial comment see page 778

Functional neuroimaging can potentially inform the discussion on vascular dementia by better defining pathophysiological mechanisms. In AD, reductions of regional cerebral metabolic rates of glucose (CMRglc) predominate in temporal and parietal cortex.[10-12] Positron emission tomography (PET) can also define cortical hypofunction at sites remote from cerebral infarction and thus can potentially provide a more complete picture of the effects of cerebrovascular disease on the brain than structural imaging. For these reasons we chose to use PET and the glucose metabolic tracer fludeoxyglucose F 18 to

SUBJECTS AND METHODS

SUBJECT SELECTION AND EVALUATION

Subjects were recruited from a university dementia clinic and a Department of Veterans Affairs system of hospitals and clinics in northern California. Subjects were identified by review of computed tomographic (CT) or magnetic resonance imaging (MRI) scans and invited to participate if they had 1 or more subcortical lacunar infarcts and met entry criteria. Eligible and willing subjects subsequently underwent a thorough evaluation, consisting of a medical and neurologic evaluation and laboratory screening to exclude reversible dementias. Comprehensive neuropsychological testing included the Mini-Mental State Examination (MMSE)[13] as a measure of global cognitive function. In addition, all subjects had a research MRI scan performed. Subjects were excluded if they had cortical infarction, or if they had evidence of diseases or conditions that could affect cognitive function.

For the purposes of this study, subjects were defined clinically as "cognitively normal (CN)," "cognitively impaired (CI)," or "with dementia (D)." The diagnosis of dementia was arrived at by taking into account both medical history and neuropsychological testing and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[14] criteria were used. Subjects were judged to be cognitively impaired if they scored 0.5 on the Clinical Dementia Rating Scale[15] and showed mild cognitive decline on neuropsychological testing.

In addition to cognitive classification, subjects were categorized as having lacunae or not by a single neuroradiologist (D.N.), who was blinded to the cognitive status of the patients. All ratings of stroke were performed on MRIs obtained on a single scanner using the same imaging protocol and the same criteria for definition of a lacune.

The combination of 3 cognitive status groups times 2 stroke groups (stroke and no stroke) yielded 6 potential groups. Because this report is concerned with vascular disease, we describe the results in 3 stroke groups: subcortical stroke and normal cognitive function (S-CN), subcortical stroke and cognitive impairment (S-CI) and no dementia, and subcortical stroke and dementia (S-D); and the control group (the group without stroke or dementia).

MRI DATA

Magnetic resonance imaging was performed on a Siemens 1.5-T Magnetom VISION (Siemens, Erlangen, Germany) system equipped with a standard quadrature head coil. The imaging protocol included a sagittal T_1-weighted localizer scan, oblique axial double-spin echo scans angled parallel to the optic nerve, and a volumetric 3-dimensional magnetization prepared rapid gradient echo (MP-RAGE)–T_1 data set angled perpendicular to the double-spin echo image planes. The double-spin echo parameters were repeat time, 2500 milliseconds; first echo time, 20 milliseconds; second echo time, 80 milliseconds; 0.94-mm^2 resolution; and 48 to 51 contiguous 3-mm-thick slices covering the entire brain. The MP-RAGE parameters were repeat time, 10 milliseconds; delay time, 250 milliseconds; echo time, 4 milliseconds; flip angle, 15°; 1.0-mm^2 resolution; and 1.4-mm-thick partitions.

PET IMAGING

Fludeoxyglucose F 18–PET studies were performed on a CTI/Siemens ECAT EXACT HR PET scanner[16] within 3 months of clinical evaluation and MRI. A subset of subjects had quantitative studies using a radial artery catheter to collect a blood input function.[17] All subjects performed a continuous recognition memory task during tracer uptake[18] following injection of approximately 370 MBq of fludeoxyglucose F 18. PET scanning commenced approximately 40 minutes after tracer injection, with 40 minutes of emission data acquisition followed by a 20-minute transmission scan.

PET DATA ANALYSIS

The PET data were analyzed using procedures developed locally for the analysis of whole brain PET data sets that are described in a separate publication.[19] The approach uses 3-dimensional MRI data (MP-RAGE in this case) for anatomic-region specification and analysis of the PET data. Two-dimensional MRI slices are used to define regions of interest that are subsequently tiled together to form volumes of interest (VOIs). By coregistration of PET and MRI data sets,[20] PET counts are extracted from these VOIs and used with the arterial input function to calculate regional CMRglc.[21,22] In a final step, the VOI metabolic rates (or the count values) are adjusted for the effects of partial volume caused by cerebral atrophy using the segmented MRI data set as prior information in the manner developed by Meltzer et al.[23]

All VOIs were drawn by a single operator (L.T.K.) blinded to patient classification, using a set of rules for guiding the boundaries of the VOIs, which are shown in **Figure 1**. Regions studied included temporal cortex (superior and middle temporal gyri), dorsolateral frontal cortex, orbitofrontal cortex, inferior parietal lobe (supramarginal and angular gyri), occipital (calcarine) cortex, and hippocampus (subiculum, Ammon horn, dentate gyrus, and associated white matter tracts). Whole brain glucose metabolism was calculated by defining a VOI outlining the entire brain (both hemispheres, including posterior fossa and subcortical structures) and using the quantification and atrophy correction procedures described above to determine CMRglc. In subjects without arterial catheterization, the atrophy corrected whole brain counts were used to normalize regional atrophy corrected counts to determine relative brain metabolism. Whole brain was chosen for the normalization region because it permits regional comparisons by scaling according to global metabolism, without introducing the bias that could distort ratios when small brain regions are used for normalization.

STATISTICS

Two separate sets of variables were available for analysis. In 18 subjects, arterial blood input functions were available, and the atrophy-corrected regional CMRglc was calculated for each VOI. These values were analyzed with a repeated-measures analysis of variance (ANOVA) using group-by-regions design. In the entire group of 32 subjects, the normalized regional CMRglc ratio was also evaluated with a repeated-measures ANOVA. When the repeated-measures ANOVA was significant, follow-up 1-way ANOVAs were performed, and all such tests were corrected for multiple comparisons using the Bonferroni correction. Because groups were not matched for education, significant results were followed up with analyses that used education as a covariate. Inclusion of this covariate did not affect the results obtained.

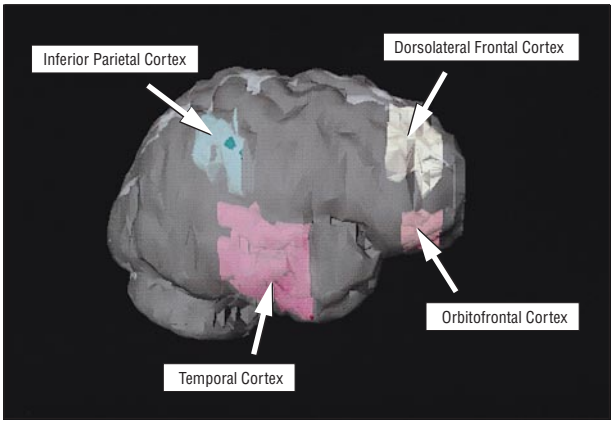

Figure 1. *Volumes of interest from a single control subject, shown as projected onto a model of the brain surface derived from the subject's magnetic resonance image. For clarity, medial cortical regions (hippocampus, calcarine cortex) are not shown.*

determine relationships between glucose metabolism and cognitive impairment in patients with subcortical infarction. Only patients with lacunar cerebral infarction in subcortical structures were studied to reduce the heterogeneity of the disorder. Furthermore, the study design eliminated problems associated with different diagnostic criteria for vascular dementia by evaluating only relationships between cognitive function, subcortical lacunar infarction, and cortical metabolism.

RESULTS

The **Table** shows the characteristics of the entire sample and the sample with arterial catheters and absolute regional CMRglc determination. There were significant differences in education across the groups, with subjects having cognitive impairments and dementia, in general, showing lower education than subjects with no cognitive impairments. Differences in total stroke numbers were significant only in the entire sample and only when control subjects with no strokes were compared with the other groups. There were no statistically significant differences in the regional distributions of lacunae across the 3 stroke groups. In particular, thalamic lacunae were no more common in subjects with dementia or cognitive impairments than in those with normal cognitive function, although the sample sizes in each subgroup were small.

Whole brain absolute CMRs of glucose are shown in **Figure 2**. Patients with S-D had the lowest CMRglc, which was only slightly lower than that of patients with cognitive impairments, while both groups were lower than the 2 groups with no cognitive impairments. The results of the ANOVA were significant ($P = .05$), with post hoc Fisher protected least significant difference tests revealing that patients with S-D had significantly ($P < .05$) lower CMRglc than both control and S-CN patients, who did not differ from one another.

Absolute regional CMRs of glucose are shown in **Figure 3** for the 4 groups. The 2 groups with no cognitive impairments show very similar patterns, which are almost superimposed and clearly higher than the 2 groups with cognitive impairments in all regions but the calcarine cortex. The ANOVA approached significance for this comparison ($P = .08$). When we combined the control and S-CN into one group and the S-CI and S-D group into another group, the repeated-measures ANOVA showed a highly significant ($P = .008$) group effect, along with a significant region effect ($P < .001$) and no interaction. This indicated that the cognitively normal subjects showed higher regional CMRglc than the subjects with cognitive impairments across multiple brain regions, consistent with the findings for whole brain CMRglc and Figure 3.

Results of the metabolic ratios are shown in **Figure 4**. Normalization of regional CMRglc eliminates the scaling effect of global CMRglc but reveals differences in the patterns in regional CMRglc. This is demonstrated by the ANOVA results that showed a borderline group effect ($P = .09$), a significant region effect ($P < .001$), and a significant interaction ($P = .02$). A series of ANOVAs for each brain region demonstrated that the right dorsolateral frontal cortex was significantly different ($P < .001$) between groups, with Fisher post hoc tests showing that all 3 stroke groups had significantly ($P < .05$) lower regional CMRglc ratios than the controls. The group effect for right dorsolateral frontal cortex remains significant when a Bonferroni correction for multiple comparisons (12) is applied using a setwise α of .05.

To evaluate the relationship between cerebral infarction, cognitive function, and glucose metabolism, we performed 3 correlations. For the entire sample, there was no significant correlation between the number of strokes and performance on the MMSE ($r = 0.14$; $P = .46$). For the group of 18 subjects who had absolute CMRglc determined, there was a higher, though still nonsignificant correlation be-

Subject Characteristics*

	Control	S-CN	S-CI	S-D
No. of patients				
Entire	11	8	5	8
Absolute	6	4	3	5
Age, y				
Entire	72.5 (8.7)	76.9 (6.9)	65.0 (5.4)	74.0 (8.1)
Absolute	70.7 (10.8)	73.8 (6.9)	67.0 (4.4)	78.2 (4.1)
Education, y				
Entire†	15.3 (3.1)	14.3 (1.9)	11.2 (5.0)	10.9 (2.3)
Absolute‡	14.8 (3.1)	13.8 (1.7)	8.7 (5.0)	10.0 (2.3)
MMSE§				
Entire	29.2 (1.5)	28.5 (1.3)	27.4 (2.7)	23.4 (4.2)
Absolute	29.8 (0.4)	28.0 (1.6)	27.3 (3.8)	22.2 (4.4)
Sex, No. of M/F				
Entire	5/6	5/3	3/2	5/3
Absolute	2/4	3/1	2/1	5/0
Lacunae, No.				
Entire‖	0 (0)	3.8 (3.2)	5.0 (1.8)	6.3 (5.6)
Absolute	0 (0)	2.8 (1.7)	4.7 (2.1)	3.5 (5.1)

**Entire indicates the entire sample; absolute, the sample with absolute metabolic rates calculated; S-CN, stroke and normal cognitive function; S-CI, stroke and cognitive impairment; S-D, stroke and dementia; and MMSE, Mini-Mental State Examination. Values are mean ± SD, except for sex. All post hoc tests are Fisher protected least significant difference.*

†Significantly different means, P<.01 (control vs S-CI and S-D and S-CN vs S-D).

‡Significantly different means, P<.05 (control vs S-CI and S-D and S-CN vs S-CI).

§Significantly different means, P<.001 (S-D vs control, S-CI, and S-CN).

‖Significantly different means, P<.001 (control vs S-D, S-CI, and S-CN).

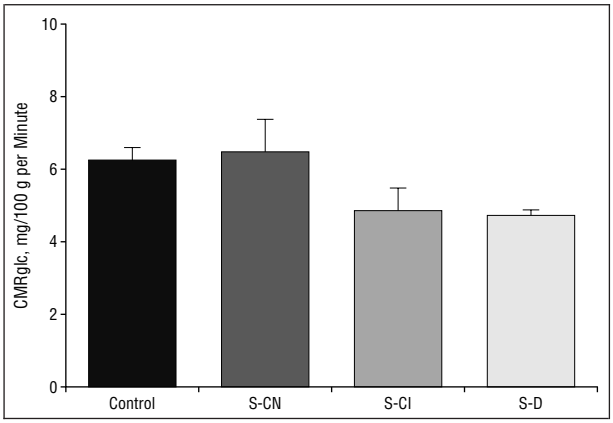

Figure 2. *Whole brain cerebral metabolic rates of glucose (CMRglc) in the 4 subject groups: controls without stroke, stroke–cognitively normal (S-CN), stroke–cognitively impaired (S-CI), and stroke with dementia (S-D). Bars indicate the mean and error bars represent the SEM.*

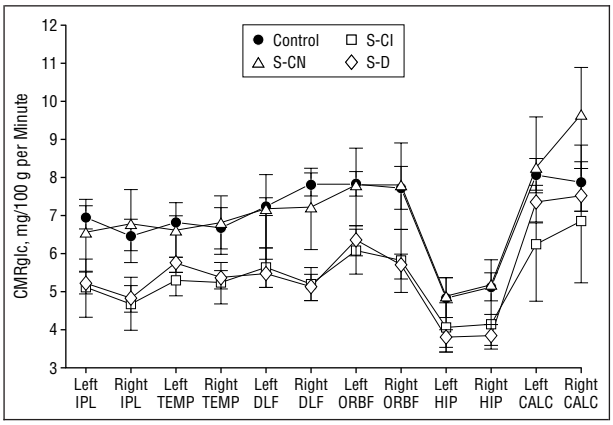

Figure 3. *Absolute regional cerebral metabolic rates of glucose (CMRglc) for the 4 subject groups: controls without stroke, stroke–cognitively normal (S-CN), stroke–cognitively impaired (S-CI), and stroke with dementia (S-D). Brain regions are left and right inferior parietal lobe (IPL), temporal lobe (TEMP), dorsolateral frontal cortex (DLF), orbitofrontal cortex (ORBF), hippocampus (HIP), and calcarine cortex (CALC). Error bars are SEM.*

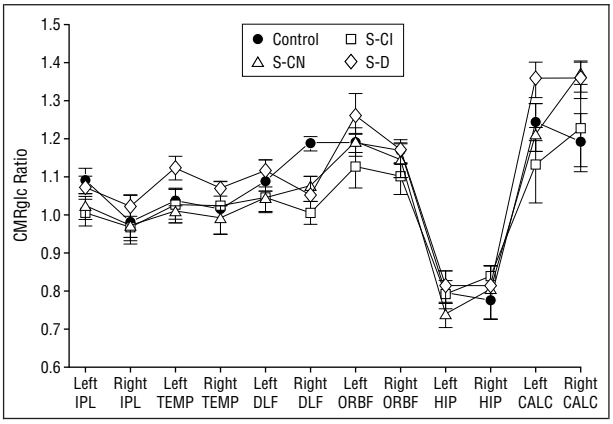

Figure 4. *Regional cerebral metabolic rates of glucose (CMRglc) normalized to whole brain CMRglc (regional CMRglc ratio) for the 4 groups: controls without stroke, stroke–cognitively normal (S-CN), stroke–cognitively impaired (S-CI), and stroke with dementia (S-D); and brain regions: left and right inferior parietal lobe (IPL), temporal lobe (TEMP), dorsolateral frontal cortex (DLF), orbitofrontal cortex (ORBF), hippocampus (HIP), and calcarine cortex (CALC). Error bars are SEM.*

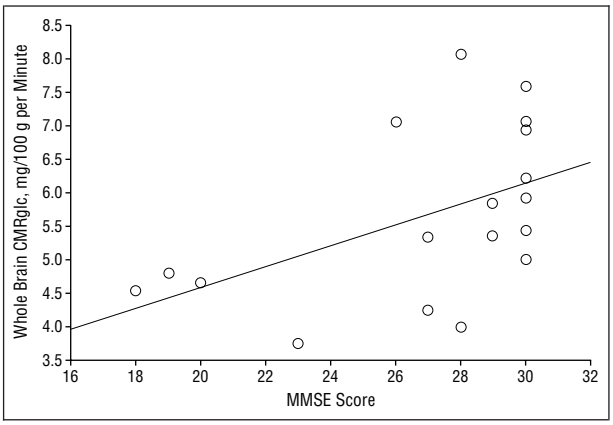

Figure 5. *Correlation between Mini-Mental State Examination (MMSE) scores and whole brain cerebral metabolic rate of glucose (CMRglc) for all 18 subjects in all 4 groups with absolute CMRglc determined.*

tween the number of strokes and whole brain CMRglc ($r = 0.36$; $P = .15$). When whole brain CMRglc was correlated with the scores on the MMSE for all 18 subjects with absolute CMRglc determined, this correlation was significant ($r = 0.50$; $P = .03$) (**Figure 5**). Removal of the 6 control subjects resulted in decrease of the correlation coefficient to 0.42, which was no longer significant ($P = .17$).

COMMENT

This study reveals a number of findings concerning the relationship between subcortical strokes and cognitive impairment. First, cognitive function is related to the overall degree of cortical glucose metabolism, with cognitively normal subjects showing higher metabolic rates overall than subjects with cognitive impairments and dementia. Furthermore, the degree of whole brain glucose metabolism is related to the degree of cognitive impairment, while the number of strokes is only weakly related to both of these factors. Finally, there appears to be a regionally specific effect of subcortical strokes on right dorsolateral frontal glucose metabolism.

The relationship between cognitive function and hypometabolism that we found is consistent with previous reports. It is well established that subcortical cerebral infarction may produce cortical hypometabolism and hypoperfusion (the phenomenon of diaschisis), especially when infarcts are located in thalamus and white matter.[24-26] However, most such studies have reported inconsistent relationships between subcortical lesions, cortical hypofunction, and behavioral deficits. Even fewer studies have related cortical physiology to behavior in patients with generalized cognitive decline, and none have specifically explored these relationships in patients with only subcortical infarcts. Mielke et al[27] found that the volume of hypometabolic regions was related to MMSE score in both patients with AD and vascular dementia, though there was no difference between the groups. This study was quite different from the present report, however, since the patients with vascular dementia had both subcortical and cortical lesions, and there was no stroke control group permitting the differentiation of the effects of stroke from those of dementia. Sultzer et al[28] also found modest relationships between the severity of subcortical white

matter lesions and degree of global hypometabolism and behavioral changes in a PET study of patients with subcortical cerebrovascular dementia.

Several confounding factors that may be related to dementia in stroke are accounted for in this study. Cerebral atrophy has been suggested as an independent risk factor for dementia in patients who have had a stroke.[29-31] Because the effects of atrophy were minimized in this study, metabolism, independent of brain structure, appears to be associated with cognitive failure. Advanced age has also been associated with the development of dementia in stroke patients in many studies, as has lower education in some studies.[32-35] Our subject groups did not differ by age, and although the group with stroke and mild cognitive impairment was somewhat younger, this was not significant. Furthermore, this slight age difference is unlikely to bias the results since age has relatively small, if any, effects on glucose metabolism over small age ranges[36,37] and would result in lower metabolic rates in younger subjects, contrary to our findings in the S-CI group. It is also unlikely that education differences affected the results, since statistical correction for group differences did not change the findings.

It is interesting that the cognitive status of subjects appeared to be better related to cortical glucose metabolism than to the number of subcortical strokes. The number of strokes did not differ significantly between the groups and there were not strong correlations between MMSE and the number of strokes. This finding is congruent with current conceptualizations of behavior that place the cerebral cortex in the midst of a number of circuits involving subcortical connections that mediate frontal lobe,[38,39] mnemic,[40,41] and attentional[42] functions. Thus, multiple subcortical lesions may cumulatively and synergistically[43] affect behavior through effects on cerebral cortex. However, for a variety of reasons, the simple number of lacunae may not be a determining factor in affecting these cortical circuits. For example, white matter signal hyperintensities (WMSHs), which we did not quantitate, may also exert independent effects on cortical function.[28,44,45] Subjects in this sample had a wide range of WMSH severities that could have affected cortical CMRglc. As DeCarli et al[46] have reported that individuals with such hyperintensities have reduced frontal lobe metabolism, these WMSHs in our subjects could have contributed significantly to the cortical changes, obscuring the role of lacunae. Furthermore, the criteria we used for lacunae might have missed small subcortical infarcts that could have functionally significant effects. Finally, simply attempting to count lacunae is probably an overly simplistic way to detect their effects on cognition, since these effects are likely related to size and location, with some lesions more likely to have functionally significant effects than others. Nevertheless, as a first approximation, simple lacune number does not appear to be as strongly related to cognitive function as does cortical glucose metabolism.

The specific effects of subcortical lesions on right frontal lobe function may have several explanations. Subcortical lesions are well known to produce frontal lobe–type cognitive deficits,[39,47] and subcortical vascular dementia may be a particularly likely candidate to produce such frontal-subcortical syndromes.[43,48] Frontal reductions in regional cerebral blood flow, oxygen metabolism, and glucose metabolism have been seen in PET studies of patients with subcortical cerebrovascular disease.[28,44] In addition, the cognitive task performed during this PET study places demands on working memory[49] that might activate prefrontal cortex.[50-52] Regardless of the precise reason for these frontal lobe findings, it seems unlikely that a specific effect on the right frontal lobe is a necessary characteristic of this syndrome.

The global and regional effects differed by groups, with subjects having dementia showing lower global CMRglc than subjects with S-CN and controls, but all stroke subjects showing lower regional CMRglc ratios in the right frontal lobes than did controls. This suggests that global CMRglc is closely related to cognitive state, while regional CMRglc is related to the presence of strokes. It is tempting to speculate that this regional effect may be an early feature of subcortical infarction that only results in cognitive impairment after a global reduction of metabolism has been reached. This hypothesis could be tested with longitudinal observation of stroke subjects.

This study is not a definitive report of the pattern of glucose metabolic changes in patients with vascular dementia for several reasons. First, this study was designed as an assessment of the effects of subcortical lesions on cortical metabolism and cognitive function, and current diagnostic classification schemes for vascular dementia were not applied. Second, vascular dementia is heterogeneous, and is unlikely to present with a single specific pattern of hypofunction because the distribution of infarct location is variable. Multifocal patterns of hypometabolism and hypoperfusion have frequently been reported in this condition[53] and proposed to be diagnostic, but many studies report that there is no characteristic pattern of hypofunction in vascular dementia.[54,55] Third, temporal and parietal hypometabolism and hypoperfusion, similar to that seen in AD, have also been reported in vascular dementia,[28,56] which could be due either to the location of infarcts or to the coexistence of AD. In this study, the pattern of reduced glucose metabolism seen in patients with dementia was not that of temporoparietal hypometabolism. In fact, in the entire stroke group, this pattern of temporoparietal hypometabolism was only seen on visual inspection in 1 subject. While we do not propose a charactertistic pattern of hypometabolism in vascular dementia as an interpretation of our data, it is interesting to note that temporal and parietal hypometabolism were not specifically seen in subjects with dementia, providing some evidence that AD is not invariably the explanation of cognitive decline in subjects with stroke. However, DeCarli et al[57] have suggested that subcortical cerebrovascular disease in patients with AD may make the predominant temporoparietal AD pattern less distinctive by also depressing frontal lobe metabolism. These discussions must remain conjectural until neuropathological verification of the cause of dementia is obtained.

While the mechanism underlying dementia in patients with subcortical cerebrovascular disease is undoubtedly complex, this study clearly demonstrates that patients with subcortical infarction who are cognitively

intact have higher metabolic rates than those with cognitive dysfunction. In addition, subtle changes in frontal lobe function can be detected in such patients, even those with normal cognition. These studies support the notion that the production of dementia in subcortical vascular disease is related to both global and regional effects on cortical metabolism that are in turn related to the clinical presentation of the patient.

Accepted for publication October 23, 1998.

This study was supported by the National Institute on Aging, Bethesda, Md, grants AG12435 and AG10129.

Reprints: William J. Jagust, MD, Department of Neurology, University of California, Davis Medical Center, 4860 Y St, Suite 3700, Sacramento, CA 95817 (e-mail: wjjagust @ucdavis.edu).

REFERENCES

1. Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. *J Neurol Sci*. 1970;11:205-242.
2. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia: a cause of mental deterioration in the elderly. *Lancet*. 1974;2:207-209.
3. Chui HC, Victoroff JI, Margolin DI, Jagust WJ, Shankle WR, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer disease diagnostic and treatment centers. *Neurology*. 1992;42:473-480.
4. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
5. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. *JAMA*. 1989;262:2551-2556.
6. Sulkava R, Wikstrom J, Aromaa A, et al. Prevalence of severe dementia in Finland. *Neurology*. 1985;35:1025-1029.
7. Gearing M, Mirra SS, Hedreen JC, Sumi SM, Hansen LA, Heyman A. The Consortium to Establish a Registry of Alzheimer's Disease (CERAD), part X: neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology*. 1995;45:461-466.
8. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *JAMA*. 1997;277:813-817.
9. Erkinjuntti T. Types of multi-infarct dementia. *Acta Neurol Scand*. 1987;75: 391-399.
10. Benson DF, Kuhl DE, Hawkins RA, Phelps ME, Cummings JL, Tsai SY. The fluorodeoxyglucose 18F scan in Alzheimer's disease and multi-infarct dementia. *Arch Neurol*. 1983;40:711-714.
11. Friedland RP, Budinger TF, Ganz E, et al. Regional cerebral metabolic alterations in dementia of the Alzheimer type: positron emission tomography with [18F]fluorodeoxyglucose. *J Comput Assist Tomogr*. 1983;7:590-598.
12. Foster NL, Chase TN, Mansi L, et al. Cortical abnormalities in Alzheimer's disease. *Ann Neurol*. 1984;16:649-654.
13. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-198.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
15. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412-1414.
16. Wienhard K, Dahlbom M, Eriksson L, et al. The ECAT EXACT HR: performance of a new high resolution positron scanner. *J Comput Assist Tomogr*. 1994;18:110-118.
17. Jagust WJ, Eberling JL, Richardson BC, et al. The cortical topography of temporal lobe hypometabolism in early Alzheimer's disease. *Brain Res*. 1993;629:189-198.
18. Paller KA, Acharya A, Richardson BC, et al. Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. *J Cogn Neurosci*. 1997;9:277-293.
19. Klein GJ, Teng X, Jagust WJ, et al. A methodology for specifying PET VOIs using multimodality techniques. *IEEE Trans Med Imaging*. 1997;16:405-415.
20. Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr*. 1993;17:536-546.
21. Sokoloff L, Reivich M, Kennedy C, et al. The (14C) deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. *J Neurochem*. 1977;28:897-916.
22. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol*. 1979;6:371-388.
23. Meltzer CC, Leal JP, Mayberg HS, Wagner HN, Frost JJ. Correction of PET data for partial volume effects in human cerebral cortex by MR imaging. *J Comput Assist Tomogr*. 1990;14:561-570.
24. Baron JC, D'Antona R, Pantano P, Serdaru M, Samson Y, Bousser MG. Effects of thalamic stroke on energy metabolism of the cerebral cortex. *Brain*. 1986; 109:1243-1259.
25. Perani D, Vallar G, Cappa S, Messa C, Fazio F. Aphasia and neglect after subcortical stroke. *Brain*. 1986;110:1211-1229.
26. Pappata S, Mazoyer B, Tran Dinh S, Cambon H, Levasseur M, Baron JC. Effects of capsular or thalamic stroke on metabolism in the cortex and cerebellum: a positron tomography study. *Stroke*. 1990;21:519-524.
27. Mielke R, Herholz K, Grond M, Kessler J, Heiss W-D. Severity of vascular dementia is related to volume of metabolically impaired tissue. *Arch Neurol*. 1992; 49:909-913.
28. Sultzer DL, Mahler ME, Cummings JL, Van Gorp WG, Hinkin CH, Brown C. Cortical abnormalities associated with subcortical lesions in vascular dementia. *Arch Neurol*. 1995;52:773-780.
29. Ladurner G, Iliff LD, Lechner H. Clinical factors associated with dementia in ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 1983;45:97-101.
30. Loeb C, Gandolfo C, Bino G. Intellectual impairment and cerebral lesions in multiple cerebral infarcts. *Stroke*. 1988;19:560-565.
31. Tatemichi TK, Foulkes MA, Mohr JP, et al. Dementia in stroke survivors in the Stroke Data Bank cohort: prevalence, incidence, risk factors, and computed tomographic findings. *Stroke*. 1990;21:858-866.
32. Tatemichi TK, Desmond DW, Paik M, et al. Clinical determinants of dementia related to stroke. *Ann Neurol*. 1993;33:568-575.
33. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disase in a defined elderly Japanese population: the Hisayama Study. *Neurology*. 1995;45:1161-1168.
34. Kokmen E, Whisnant JP, O'Fallon WM, Chu C-P, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960-1984). *Neurology*. 1996;46:154-159.
35. Gorelick PB. Status of risk factors for dementia associated with stroke. *Stroke*. 1997;28:459-463.
36. Duara R, Margolin RA, Robertson-Tchabo EA, et al. Cerebral glucose utilization as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. *Brain*. 1983;106:761-775.
37. Yoshii F, Barker WW, Chang JY, et al. Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. *J Cereb Blood Flow Metab*. 1988;8:654-661.
38. Alexander GE, DeLongh RM, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci*. 1986;9:357-381.
39. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol*. 1993; 50:873-880.
40. Squire LR. Mechanisms of memory. *Science*. 1986;232:1612-1619.
41. Fazio F, Perani D, Gilardi MC, et al. Metabolic impairment in human amnesia: a PET study of memory networks. *J Cereb Blood Flow Metab*. 1992;12:353-358.
42. Mesulam M-M. A cortical network for directed attention and unilateral neglect. *Ann Neurol*. 1981;10:309-325.
43. Wolfe N, Linn R, Babikian VL, Knoefel JE, Albert ML. Frontal systems impairment following multiple lacunar infarcts. *Arch Neurol*. 1990;47:129-132.
44. Yao H, Sadoshima S, Kuwabara Y, Ichiya Y, Fujishima M. Cerebral blood flow and oxygen metabolism in patients with vascular dementia of the Binswanger type. *Stroke*. 1990;21:1694-1699.
45. Herholz K, Heindel W, Rackl A, et al. Regional cerebral blood flow in patients with leuko-araiosis and atherosclerotic carotid artery disease. *Arch Neurol*. 1990; 47:392-396.
46. DeCarli C, Murphy DGM, Tranh M, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995;45:2077-2084.
47. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. *Neurology*. 1989;39:349-354.
48. Jagust WJ, Budinger TF, Reed BR. The diagnosis of dementia with single photon emission computed tomography. *Arch Neurol*. 1987;44:258-262.
49. Baddeley A. Working memory. *Science*. 1992;255:556-559.
50. McCarthy G. Functional neuroimaging of memory. *Neuroscientist*. 1995;1: 155-163.
51. Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RSJ, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*. 1994;368:633-635.
52. Cohen JD, Perlstein WM, Braver TS, et al. Temporal dynamics of brain activation during a working memory task. *Nature*. 1997;386:604-607.
53. Deisenhammer E, Reisecker F, Leblhuber F, et al. Single photon emission computed tomography (SPECT) and x-ray CT in patients with dementia. *Psychiatry Res*. 1989;29:443-445.
54. Duara R, Barker W, Loewenstein D, Pascal S, Bowen B. Sensitivity and specificity of positron emission tomography and magnetic resonance imaging studies in Alzheimer's disease and multi-infarct dementia. *Eur Neurol*. 1989;29(suppl 3):9-15.
55. Eberling JL, Jagust WJ, Reed BR, Kwo-on-Yuen PF, Martin EM. Single-photon emission computed tomography studies of regional cerebral blood flow in multiple infarct dementia. *J Neuroimaging*. 1992;2:79-85.
56. Holman BL, Johnson KA, Gerada B, Carvalho PA, Satlin A. The scintigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *J Nucl Med*. 1992;33:181-185.
57. DeCarli C, Grady CL, Clark CM, et al. Comparison of positron emission tomography, cognition, and brain volume in Alzhiemer's disease with and without severe abnormalities of white matter. *J Neurol Neurosurg Psychiatry*. 1996;60: 158-167.