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Risk Factors for Incident Dementia After Stroke: Role of Hypoxic and Ischemic Disorders

Moroney, J.T. MD, MRCPI; Bagiella, E. MS; Desmond, D.W. PhD; Paik, M.C. PhD; Stern, Y. PhD; Tatemichi, T.K. MD*

Author Information

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From the Departments of Neurology (J.T.M., D.W.D., T.K.T.) and Psychiatry (Y.S.), the Division of Biostatistics (E.B., M.C.P.), and the Gertrude H. Sergievsky Center (Y.S., T.K.T.), Columbia University, College of Physicians and Surgeons, New York, NY.
*Dr Tatemichi died April 22, 1995.
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Reprint requests to Dr D.W. Desmond, Stroke and Aging Research Project, Neurological Institute, 710 W 168th St, New York, NY 10032. E-mail dwd2@columbia.edu.

Abstract

Background and Purpose: Stroke significantly increases the risk of dementia in the elderly, yet the risk factors for incident dementia after ischemic stroke are not well understood. We attempted to determine whether hypoxic-ischemic (HI) disorders, which may result from comorbid medical conditions (eg, seizures, cardiac arrhythmias, pneumonia), would be an independent risk factor for the development of new dementia after stroke.

Methods: We prospectively followed 185 initially nondemented patients with ischemic stroke (age, 70.3+/-7.7 years) for a maximum of 52.8 months. We diagnosed the presence of dementia at annual examinations based on neuropsychological testing and modified DSM-III-R criteria. HI disorders were identified by record review or examination during hospitalization. We used Kaplan-Meier analysis to determine the cumulative proportion of patients with and without HI disorders who survived free of dementia and used Cox models to estimate the relative risk of dementia associated with HI disorders.

Results: The cumulative proportion (+/-SE) surviving without dementia was 51.7+/-10.9% in the HI group versus 78.2+/-4.3% in the non-HI group after 52.8 months of observation. The relative risk of incident dementia associated with HI events was 4.3 (95% confidence interval=1.9 to 9.6) after we adjusted for demographic factors, recurrent stroke, and baseline cognitive function.

Conclusions: We conclude that HI disorders may be a significant independent risk factor for incident dementia after stroke, even after adjustment for other recognized predictors of cognitive decline. Recognition of HI cerebral damage as a possible pathogenic mechanism for dementia after stroke may allow targeted therapeutic interventions to prevent subsequent cognitive deterioration.

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Key Words: cerebral infarction, cerebral ischemia, global, dementia, hypoperfusion, hypoxia

Selected Abbreviations and Acronyms

BFAS = Blessed Functional Activity Scale

CBF = cerebral blood flow

CI = confidence interval

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised

HI = hypoxic-ischemic

IR = incidence rate

MMSE = Mini-Mental State Examination

PET = positron emission tomography

RR = relative risk

VaD = vascular dementia

Dementia is a frequent consequence of cerebrovascular disease and represents a major public health problem in the United States. [1] In our own studies, we diagnosed dementia in 26.3% of patients examined 3 months after ischemic stroke, with cerebrovascular disease judged to be the primary underlying mechanism in 56.1% of those cases, [2] and we have found that ischemic stroke significantly increased the long-term risk of developing dementia among patients initially found to be nondemented. [3] Few studies have investigated the risk factors for incident dementia after ischemic stroke, however, even though the identification of significant risk factors could provide an avenue for targeted therapeutic interventions to prevent cognitive deterioration.

During the course of a prospective study designed to identify risk factors for cognitive decline and incident dementia after ischemic stroke, a review of the published literature and our own clinical observations suggested to us that stroke-related cognitive deficits can worsen with the development of comorbid medical disorders associated with global cerebral HI, such as seizures, sepsis, cardiac arrhythmias, and congestive cardiac failure. [3] Such HI disorders have been invoked as a possible underlying mechanism for a form of VaD termed "hypoperfusion dementia," [4] a syndrome in which the metabolic demands of the brain exceed the available cerebral blood supply, resulting in "supply failure." Although most discussions of the pathogenesis of VaD have emphasized the role of atherosclerosis and thromboembolism, supply failure may be an important additional pathogenic mechanism in certain subgroups of patients. [5] In the present study we attempted to determine whether the occurrence of such HI events in stroke patients would be an independent risk factor for the development of new dementia.

Subjects and Methods

Subjects

Subjects for this study were recruited among patients consecutively admitted within 30 days of onset of ischemic stroke to Columbia-Presbyterian Medical Center. Eligible patients were aged >or=to60 years with the diagnosis of acute ischemic stroke of any type. Index ischemic stroke was defined as the acute onset of a focal neurological deficit attributable to vascular disease of the brain and supported by CT scan (normal or relevant infarct) performed within 1 week of symptom onset. Patients with a history of prior cerebral ischemic events were included, although patients with severe aphasia were excluded if they scored [6] Additional exclusions were the presence of a concomitant central nervous system disorder potentially affecting cerebral function (eg, Parkinson's disease), primary language other than English or Spanish, or severe medical comorbidity (eg, terminal cancer) limiting survival over the planned follow-up period of 5 years. We obtained informed consent from subjects or their family members using procedures approved by the Institutional Review Board of Columbia-Presbyterian Medical Center.

During hospitalization medical and neurological histories were collected, and each patient underwent structured neurological examinations and cognitive assessments with the use of the MMSE [7] and functional assessments with the use of the Barthel Index [8] and the BFAS. [9] Using the BFAS, we interviewed patients, family members, and/or other key informants to determine whether functional deficits were evident before the index stroke. A more extensive description of our recruitment procedures is available in an earlier publication on methods and baseline findings. [2] Among the 297 patients who were initially enrolled, 251 received assessments that were adequate for the determination of dementia status 3 months after stroke. Among these 251 patients, 66 were judged to have dementia and were excluded from this analysis. Their clinical features have been described previously. [10] The remaining 185 nondemented patients constituted the stroke cohort for this incidence study.

Diagnosis of HI Disorders

The HI category of disorders was defined on the basis of previous reports, [11,12] and data were gathered on all medical disorders that could result in cerebral HI as well as all other intercurrent illnesses and hospitalizations. Data collection was blinded to the diagnosis of incident dementia. The number of reported HI disorders was large and included cardiopulmonary arrest, cardiac arrhythmias, congestive heart failure, myocardial infarction, syncope, seizures, sepsis, pneumonia, respiratory failure, drug overdosage, burns, hypotension with general anesthesia, profound hypoglycemia, hanging, and strangulation. Some of the reported HI conditions were underrepresented or absent in our sample (eg, drug overdosage and hypotension with general anesthesia), and other conditions (eg, cardiopulmonary arrest) were not included in the HI category because all of the patients in our cohort who experienced that event subsequently died and were not available for follow-up neuropsychological evaluation. We did not rely on specific diagnostic criteria for each HI condition but instead relied on the clinical judgment of the admitting physician. As such, we recognize the possibility of misdiagnosis due to variability between physicians in the interpretation of clinical information.

Diagnostic Criteria for Dementia

Three months after the onset of stroke, patients were given a battery of neuropsychological tests developed for the purpose of diagnosing dementia in a bilingual (English and Spanish), multiethnic, elderly population [13,14]; in addition, the MMSE was administered as a global measure of cognitive impairment but not for the purpose of dementia diagnosis. Neurological and functional examinations were repeated. We chose an interval of 3 months after stroke onset for neuropsychological testing to allow sufficient time for patients to exhibit a stable course. [15,16]

All available information gathered from the neurological, neuropsychological, and functional assessments administered at the 3-month visit was reviewed at a diagnostic case conference attended by the examining neurologist and two neuropsychologists experienced in the diagnosis of dementia; if any two raters disagreed, the judgment of the third rater was sought and consensus achieved. Dementia was diagnosed according to modified DSM-III-R criteria, [17] consistent with a Clinical Dementia Rating score of >or=to1. [18] Our criteria for dementia required impairment in memory function as well as deficits in at least two other cognitive domains (ie, orientation, abstract reasoning, language, and visuospatial function), combined with functional impairment documented with the BFAS that was unrelated to physical deficits. [2] The requirement that patients exhibit deficits in memory and at least two other cognitive domains was intended to ensure that patients were not misclassified on the basis of poor performance on a single measure. To diagnose dementia in aphasic patients who were testable, impairment in nonverbal memory was required.

Impairment within each cognitive domain was defined by performance on neuropsychological tests falling below predetermined cutoff scores for each of the subtests developed from pilot data. [13] The use of cutoff scores was intended to ensure that study criteria for the diagnosis of dementia would be objective and replicable. We have reported norms for this battery in our stroke and control subjects and consider the cutoffs to be conservative. [14] Agreement on the diagnosis of dementia was excellent, with a kappa of.96 based on independent judgments by two raters in a sample of 63 patients.

Patient Follow-up

Patients were reexamined annually with the clinical assessments described above. Scheduling of annual examinations was based on the date of stroke onset. Each patient's interval medical history was examined to identify the occurrence of new HI disorders and other comorbid medical conditions. The exact dates of occurrence of HI disorders were recorded when available, otherwise the date of occurrence was assigned to the midpoint of the corresponding follow-up interval. If more than one HI disorder had occurred we used the date of the event closest to that of the next scheduled evaluation. Whenever possible, patients were given medical and neurological examinations during their hospitalization, and their medical records were reviewed. However, the timing of the annual neuropsychological evaluations was based on the date of onset of the index stroke and not on intercurrent hospitalizations. To maximize follow-up rates, we made visits to patients' homes or healthcare facilities if they were unable or unwilling to visit the medical center, and we did not consider them as having refused any interval examination until at least four attempts had been made to contact and examine them. When in-person examinations were not possible, we obtained information by telephone to asccrtain vital status and the occurrence of major clinical events.

We used the same diagnostic procedure outlined above to diagnose incident dementia. For the list-learning task administered as part of the neuropsychology battery, different word lists of equivalent difficulty were used in follow-up visits to minimize practice effects; otherwise, the test battery remained identical. We did not require a specific degree of decrement in performance for the diagnosis of incident dementia; only performance falling below the cutoff scores combined with functional impairment was required. These operationalized criteria for the diagnosis of dementia were intended to maximize consistency and reliability in diagnosis over time. [19] When dementia was diagnosed, the date of the annual visit was used as the date of onset of new dementia. Each patient was followed until death or June 30, 1993, the end of the incidence study period.

Statistical Methods

Univariate analyses with chi^2 tests of association were used for descriptive purposes to compare the 34 patients who experienced HI disorders with the 151 patients without a history of HI disorders. The reference patient group included those with non-HI comorbid medical conditions and those without any coexisting medical conditions. The crude IR of new dementia, stratified by the occurrence of HI disorders, was calculated by life-table methods. Kaplan-Meier survival analysis [20] was used to determine the cumulative proportion of subjects surviving free of dementia in the two groups. Although we diagnosed dementia at the 3-month examination, survival time was calculated from the date of stroke onset. For the purposes of the Kaplan-Meier analysis, HI time at risk was defined as the period between stroke onset and diagnosis of dementia, and reasons for censoring in this univariate and subsequent multivariate analyses included death unrelated to dementia, subject dropout, or reaching the end of the study period.

Since the Kaplan-Meier product limit technique cannot adjust for the effects of other factors or account for the timing of the HI events, we also performed Cox proportional hazards analyses [21] to estimate the RR of incident dementia associated with the occurrence of HI disorders. We fitted Cox proportional hazards models, in which the occurrence of HI disorders was treated as a time-dependent covariate, and adjusted for the effects of demographic variables and other potentially relevant factors. The following variables were included in the Cox model together with the occurrence of HI events: age (>or=to80 and 70 to 79 years versus 60 to 69 years), education (or=to13 years), race (white versus nonwhite), and sex (women versus men). Age and education were treated as trichotomous categorical variables to facilitate interpretation of the RR by substrata.

The MMSE score was also included as a measure of global cognitive function to adjust for baseline cognitive impairment but was not intended to signify the presence or absence of dementia. MMSE scores were taken from examinations performed 7 to 10 days after stroke (n=153) or, if the 7- to 10-day scores were not available, from examinations performed 30 days (n=24) or 3 months (n=8) after stroke. In addition, stroke recurrence during the follow-up period was included as a time-dependent covariate.

Results

Characteristics of Patient Sample

Clinical characteristics stratified by HI status are presented in Table 1. The only significant difference on demographic variables between the patients with HI disorders and those without was with regard to race, with HI events occurring more frequently in white relative to non-white patients (chi^2=4.04, P=.04). Among vascular risk factors, a history of cardiac disease was recorded more frequently in the patients with HI disorders (chi^2=6.26, P=.01). For cardiac disease, we used a combined category representing a broad range of cardiac diseases (angina, myocardial infarction, congestive cardiac failure, cardiac arrhythmias, and valvular heart disease). There were no significant differences between the two patient groups with regard to stroke location or subtype.

	HI Disorder (n=34)	No HI Disorder (n=151)	P*
Age, y	69.9±8.7	70.4±7.5	.78
Education, y	11.1±4.3	10.3±4.8	.41
Sex, % male	47.1	48.3	.89
Race, % nonwhite	47.1	65.6	.04
Hypertension, % yes	67.7	75.5	.34
Diabetes, % yes	26.5	31.8	.54
Hypercholesterolemia, % yes	23.5	16.6	.34
Cardiac disease, % yes	64.7	41.1	.01
Cigarette smoking, % ever smoked	64.7	58.0	.47
Stroke location, %			
Cortical	61.8	48.3	.22
Subcortical	23.5	23.2	
Brain stem/cerebellum	14.7	28.5	
Stroke subtype, %			
Atherothrombotic	17.6	20.9	.28
Embolic	35.3	20.9	
Lacunar	20.6	32.4	
Cryptogenic	26.5	25.7	

*Based on *t* tests for continuous data and χ^2 analyses for categorical data.

Table 1. Characteristics of Patients With and Without HI Events

The clinical characteristics of the 12 patients whose onset of new dementia was found to follow the development of HI disorders at the subsequent examination are summarized in Table 2. New onset cardiac disease was present in 6 (50%) of the cases, including cardiac failure (n=4), arrhythmias (n=1), and myocardial infarction (n=1). Generalized seizures were the next most frequent condition, occurring in 3 (25%) of the patients. Pneumonia was the comorbid condition temporally related to the dementia in 2 (16.7%) of the patients. Sepsis was present in 1 patient (8% of the sample). The MMSE scores at 7 to 10 days after stroke are included as a measure of baseline cognitive impairment, but it should be emphasized that the diagnosis of incident dementia was based on findings from the follow-up neuropsychological and functional examinations. All subjects had been judged to be functionally independent before the initial stroke, as determined by BFAS ratings.

Pt	Age, y/Sex	Initial Stroke Location	MMSE Score*	Recurrent Stroke	HI Disorder
1	67/M	L parietal	26	Yes	Seizure
2	61/M	L parietal	16	No	Seizure
3	76/M	L frontal	13	No	Pneumonia
4	81/F	L cerebellar	22	No	Arrhythmia
5	88/F	R capsule	22	No	CHF
6	74/F	R frontal	26	Yes	Seizure
7	68/M	R parietal-occipital	16	Yes	CHF
8	79/M	L temporal-parietal	28	No	Pneumonia
9	91/M	L frontal	18	No	MI
10	66/F	R occipital	28	Yes	Sepsis
11	67/F	L basal ganglia-capsule	19	No	CHF
12	76/M	L temporal-parietal	27	No	CHF

Pt indicates patient; L, left; R, right; CHF, congestive heart failure; and MI, myocardial infarction.
*MMSE at 7 to 10 or 30 days after stroke (not used for the purpose of dementia diagnosis).

Table 2. Clinical Characteristics of Stroke Patients With HI Disorders and Incident Dementia

Univariate Analyses

Among the 185 initially nondemented patients, 154 (83.2%) completed at least one visit after the baseline, 132 (71.4%) completed at least two visits, 73 (39.5%) completed at least three visits, and 26 (14.1%) completed at least four visits. Death occurred in 34 patients (18.4%), and 39 (21.1%) were lost to follow-up. Median follow-up for the cohort was 25.0 months, with a maximum follow-up of 52.8 months. When deaths occurring before each planned follow-up visit are excluded, the proportion of patients examined among those at risk of incident dementia was 83.2% at year 1, 88.1% at year 2, 88.8% at year 3, and 90.8% at year 4. During 427 person-years of follow-up, a total of 36 patients were found to have new dementia, resulting in an IR of 8.4 cases per 100 person-years. The unadjusted IR of dementia for the patients with a history of HI disorders was 13.0 cases per 100 person-years compared with an IR of 7.2 cases per 100 person-years for the patients free of these disorders.

As presented graphically in the Figure 1, the cumulative proportion (+/-SE) of patients surviving free of incident dementia in the HI event group was 51.7+/-10.9% versus 78.2+/-4.3% in the patients without a history of HI disorders after 52.8 months of observation time. We did not calculate a log-rank test for the survival curves between the two groups, since the log-rank does not account for the time dependency of the HI variable. A univariate Cox model is the more appropriate test in this situation and showed a significant difference between the two groups (likelihood ratio test, chi^2=13.2, P=.0003).

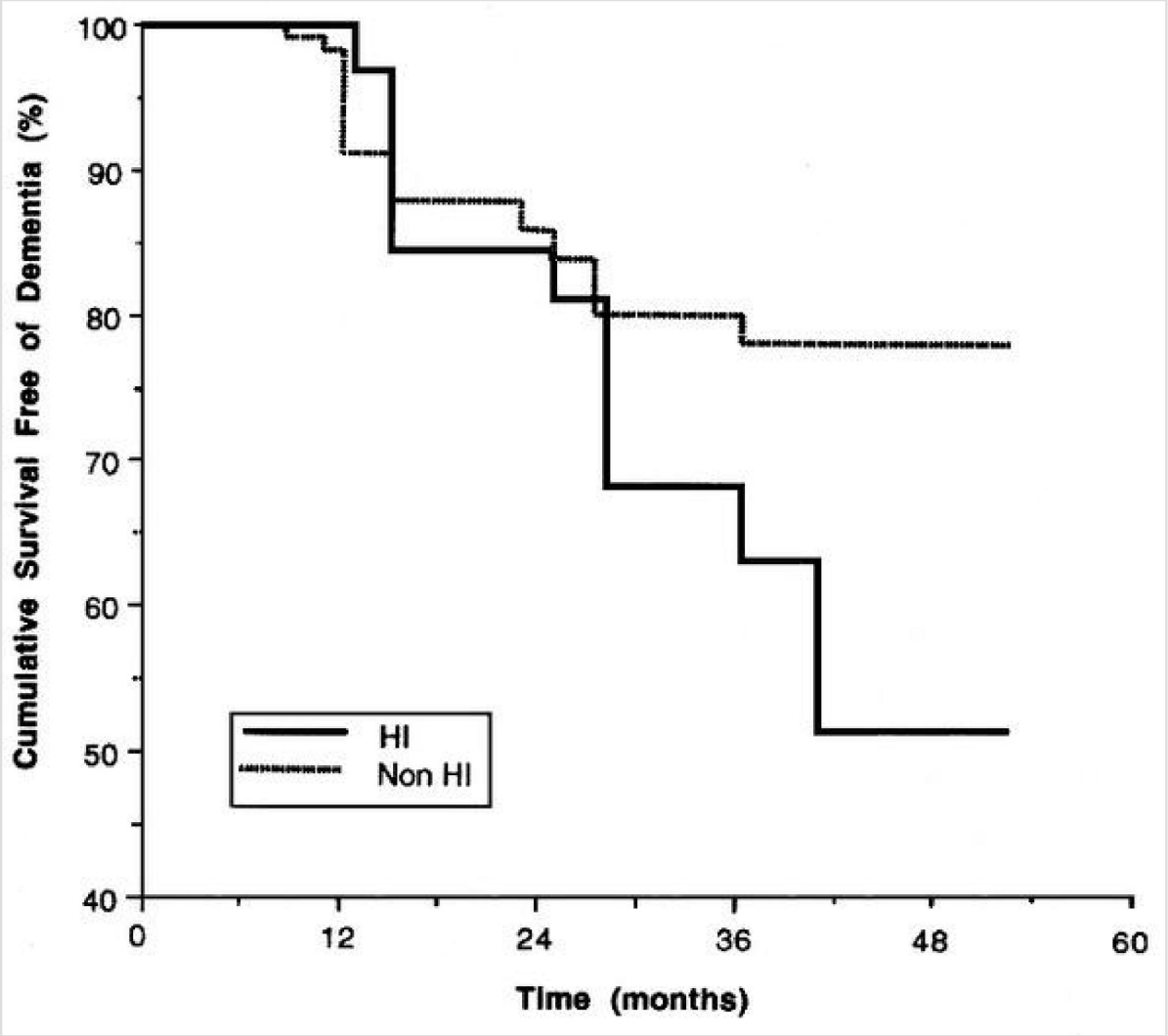

Figure 1. Kaplan-Meier analysis showing the cumulative proportion of patients surviving free of dementia stratified by HI status during the follow-up period up to 53 months.

Multivariate Analyses

The initial Cox model was based on the four demographic variables alone and revealed a significant independent effect of age on the risk of incident dementia. For the group aged >or=to80 years compared with the group aged 60 to 69 years, the RR was 3.62 (95% CI=1.31 to 10.01). As presented in Table 3, model A, when the occurrence of HI disorders was added to this basic demographic model, the RR associated with older age increased to 4.69 (95% CI=1.64 to 13.44), with a significant independent effect associated with HI disorders (RR=5.29, 95% CI=2.52 to 11.11). Education, sex, and race were not significant factors in this model.

	RR (95% CI)	
Variable	**Model A**	**Model B**
HI events (yes vs no)*	5.29 (2.52-11.11)	4.28 (1.92-9.55)
Age (vs 60-69 y)		
70-79 y	2.47 (1.10-5.52)	2.66 (1.17-6.06)
≥80 y	4.69 (1.64-13.44)	3.80 (1.25-11.60)
Education (vs ≥13 y)		
≤8 y	1.46 (0.56-3.82)	0.89 (0.31-2.57)
9-12 y	2.10 (0.75-5.86)	1.24 (0.39-3.89)
Sex (women vs men)	0.82 (0.40-1.67)	0.84 (0.39-1.80)
Race (white vs nonwhite)	0.44 (0.19-0.99)	0.47 (0.20-1.13)
Recurrent stroke (yes vs no)*		1.72 (0.72-4.11)
MMSE† (>24 vs ≤24)		3.55 (1.72-7.33)

*Time-dependent covariate.
†MMSE at 7 to 10 or 30 days after stroke (not used for the purpose of dementia diagnosis).

Table 3. RR of Incident Dementia Based on Cox Proportional Hazards Models for HI Stroke Patients Compared With Non-HI Stroke Patients Adjusting for Demographic Factors (Model A) and Demographic Factors Plus Baseline MMSE Score and Recurrent Stroke as a Time-Dependent Covariate (Model B)

To adjust for the effects of recurrent stroke and baseline cognitive status, we added stroke recurrence and MMSE score at 7 to 10 days after stroke to the model, as shown in Table 3, model B. The Cox analysis including these variables resulted in an RR of 4.28 (95% CI=1.92 to 9.55) for HI disorders as a predictor of incident dementia, while we adjusted for other significant predictors. Age remained a significant covariate, with patients aged 70 to 79 and >or=to80 years being at increased risk (RR=2.66, 95% CI=1.17 to 6.06, and RR=3.80, 95% CI=1.25 to 11.60, respectively) relative to the reference group aged 60 to 69 years. MMSE score was also significant in the final model, with an RR of 3.55 (95% CI=1.72 to 7.33), while stroke recurrence was not. Interestingly, when we added a term representing the interaction of age and HI status to the final model, we found that it was significant for subjects aged >or=to80 years (P=.049), but the small number (n=3) of older patients who experienced HI disorders and new dementia limited our ability to draw reliable conclusions. We also repeated the analysis beginning timing at 3 months after stroke onset, at which time all patients were judged to be nondemented. We developed a comparable final model in which the RR of dementia associated with HI disorders remained significant (RR=4.28, 95% CI=1.90 to 9.21) after we adjusted for demographic factors, recurrent stroke, and baseline cognitive function.

Discussion

While it is known that ischemic stroke significantly increases the risk of incident dementia, few studies have identified specific risk factors for incident dementia after stroke, and the general assumption has been that the relevant risk factors would correspond to those previously identified for stroke. [22] We found in this prospective study that the incidence of dementia was approximately doubled among stroke patients with HI disorders relative to stroke patients without such disorders. Those HI disorders remained an independent risk factor for the development of new dementia after we controlled for stroke recurrence and the baseline cognitive status of the study subjects. Although the numbers of incident dementia cases were small in the two patient groups, our findings nevertheless suggest that HI damage from cerebral hypoperfusion might be a contributing pathogenetic mechanism for dementia after stroke and that hypoperfusion or hemodynamic dementia may be more common than previously reported. We observed a particularly elevated risk of new dementia in older patients with HI disorders, suggesting increasing vulnerability to those disorders with advancing age.

Other investigators have examined the association between HI disorders and dementia in stroke patients. Sulkava and Erkinjuntti [23] reported six cases from a consecutive series of 133 patients with VaD whose onset of dementia was judged to have been temporally related to cerebral hypoperfusion. Systemic arterial hypotension with cardiac arrhythmias (ie, bradycardia, ventricular tachycardia, ventricular fibrillation, and atrial fibrillation) was documented in all six cases. Five of the six patients did not exhibit focal neurological signs but were described as confused on the initial evaluation. CT brain imaging demonstrated white matter lesions in five of the six subjects, verified at autopsy by vascular changes in the deep white matter, and atheromatous disease affecting the circle of Willis in three of the patients. The authors speculated that atherosclerosis of the deep penetrating arteries predisposed to hypoperfusion of the white matter in the setting of a fall in systemic blood pressure.

Pathological examination of 175 consecutive autopsy cases of dementia found evidence for hypoperfusion in 17 of 59 (29%) of the VaD group and 21 of 63 (33%) of the mixed dementia group. [24] The predominant pathological feature in the hypoperfusion group was incomplete infarction of the white matter, with completed infarction of the border zone territories found in only four cases. No occlusions were noted in the hypoperfusion group, but atherosclerotic narrowing of the penetrating cerebral arterioles was common. Fluctuations in the systemic intra-arterial pressure combined with atheromatous changes of the deep penetrating vessels were proposed to account for the white matter changes.

Mitchinson, [25] in a retrospective analysis of 145 stroke patients, found that hypotension was judged to have contributed to cerebral ischemia in 7 of 48 (14.6%) patients aged >60 years and in 28 of 72 (38.9%) >70 years. The hypotensive conditions identified in these patients included congestive cardiac failure, cardiac arrhythmias, pulmonary embolism, gastrointestinal hemorrhage, and sepsis. While intracranial cerebral atherosclerosis was described as common in these patients, significant extracranial carotid stenosis was found in only one of them. The author concluded that systemic hypotension superimposed on atherosclerotic changes of the cerebral penetrating arterioles resulted in cerebral hypoperfusion and ischemic cerebral damage.

Cooper and Mungas [26] found that a history of general anesthesia was significantly associated with VaD and proposed a pathophysiological role for hypotension resulting from anesthesia in the development of VaD. A history of hypertension was also associated with VaD in this study. Chronic hypertension results in the delivery of higher pressure loads to the cerebral vascular bed, forcing structural remodeling, accelerating atherogenesis, and impairing autoregulatory efficiency. [27] While antihypertensive therapy is thought to prevent progression of pathological changes in cerebral blood vessels, [28] the optimal range of blood pressure control after acute stroke is unclear. Irie et al [29] have reported a J-curve phenomenon with regard to the relation between poststroke blood pressure and stroke recurrence rates, and cognitive decline in hypertensive patients with VaD has been associated with reduction of systolic blood pressure <135 mm Hg. [30] Nobili et al [31] found evidence for cerebral hypoperfusion in one third of neurologically asymptomatic hypertensive patients. The significantly increased frequency of white matter lesions found on brain imaging in hypertensive subjects has been attributed to hypertension-induced degenerative changes of the deep penetrating arteries. PET studies have also demonstrated significant reductions in white matter CBF associated with an increased oxygen extraction fraction and increased cerebral metabolic rate for oxygen in nondemented hypertensive patients with white matter lesions, consistent with "misery" perfusion. [32] Similar PET studies in VaD subjects have revealed profoundly depressed brain metabolism in both the cortex and white matter, and it has been proposed that the development of VaD may result from progressive ischemic injury, with a decline in cerebral oxygen metabolism. [33]

The occurrence of significant hypotension has been reported after the initiation of antihypertensive therapy in the elderly, implicating medication-induced cerebral hypoperfusion in the pathogenesis of stroke and cognitive decline. Symptoms of postural hypotension developed in six elderly patients shortly after institution of antihypertensive therapy, which progressed in one patient to frank infarction. [34] Jansen et al [35] reported that seven subjects had antihypertensive regimens either initiated or altered in the 3 weeks preceding their stroke. Furosemide, a potent diuretic, had been started in five of the subjects, and reductions in their mean arterial blood pressure ranged from 10% to 22% compared with pretreatment values. Sulkava and Erkinjuntti, [23] in their description of patients who developed new dementia in temporal association with hypotensive episodes and cardiac arrhythmias, noted that all of their patients had been receiving antihypertensive medications. Blood pressure recorded in their patients at the time of hospitalization was significantly lower than premorbid readings.

Although we did not directly address the use of antihypertensive agents in our study, it is worthy of note that 8 of the 12 subjects with HI disorders who developed new dementia were receiving regular antihypertensive therapy at the time of their hospitalization. Thus, the elderly may be at higher risk for cerebral hypoperfusion from antihypertensive medication due to blunted baroreceptor compensatory reflexes, impaired cerebral autoregulation, and atheromatous disease of the deep perforating end arteries. These factors alone or in combination may predispose patients to HI damage even with minor reductions in systemic blood pressure. Thus, overzealous treatment of hypertension in elderly stroke patients, especially those known or suspected to have intracranial atherosclerosis, is potentially harmful, outweighing the proven benefits of treatment for prevention of stroke.

The term "cardiogenic dementia" [36] was proposed for elderly demented patients with cardiac arrhythmias. It suggests that treatable, unrecognized cardiac disease can cause progressive cognitive deterioration. Reductions in CBF in patients with cognitive impairment and complete heart block have been observed. [37] After cardiac pacing, cognitive performance and CBF improved in all of the patients. Impaired memory and attention in a series of patients with cardiac syncope compared with age- and education-matched control subjects [38] suggest that even brief episodes of hypoxia may have a detrimental effect on cognition. Development of dementia has been reported after myocardial infarction, with pathological examination revealing ischemic injury to the hippocampi, subicula, and amygdala, despite the absence of clinical evidence for significant hypotension or cardiac arrest. [39] Prospective analyses in which neuropsychological testing was performed before and after surgery have documented a high incidence of cognitive decline after coronary artery bypass graft surgery. [40] Placement on the extracorporeal circulatory apparatus is associated with a reduction in CBF values and may result in cerebral hypoperfusion and thus cognitive decline.

Our study has certain limitations, including a lack of follow-up brain imaging at the time of dementia diagnosis, an absence of neuropathological data, and a sample size that limited our power to investigate the association between dementia and specific HI disorders. We are continuing to follow our original cohort and are recruiting a second cohort to replicate and extend our observations. Future studies in which PET and MR spectroscopy are used may help to define the cellular mechanisms responsible for neuronal injury in the setting of hemodynamic cerebral hypoperfusion and offer a modality to test potential neuroprotective therapeutic strategies. The optimal management of hypertension in the elderly with cerebrovascular disease deserves further study to aid in determining the range of blood pressure within which cerebral perfusion would not be compromised.

In conclusion, depleted cerebral hemodynamic and neuronal metabolic reserves in elderly subjects with cerebrovascular disease may result in increased vulnerability to cerebral HI damage due to systemic disorders. Recognition of cerebral hypoperfusion or "supply failure" as a possible pathogenic mechanism in the development of incident dementia after stroke may offer potential therapeutic opportunities to favorably influence the course in vulnerable subjects with HI insults and prevent subsequent cognitive deterioration. If cognitive impairment due to cerebrovascular disease is a spectrum ranging from an asymptomatic "brain-at-risk" stage through end-stage dementia, as suggested by Hachinski, [41] then neuroprotective strategies to limit cumulative cerebral damage due to hemodynamic cerebral hypoperfusion may prove to be worthwhile.

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REFERENCES

1. Hachinski VC. Vascular dementia: a radical redefinition. Dementia. 1994;5:130-132. Bibliographic Links | [Context Link]

2. Tatemichi TK, Desmond DW, Mayeux R, Paik M, Stern Y, Sano M, Remien RH, Williams JBW, Mohr JP, Hauser WA, Figueroa M. Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. Neurology. 1992;42:1185-1193. Bibliographic Links | [Context Link]

3. Tatemichi TK, Paik M, Bagiella E, Desmond DW, Stern Y, Sano M, Hauser WA, Mayeux R. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. Neurology. 1994;44:1885-1891. Bibliographic Links | [Context Link]

4. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaduci L, Orgogozo JM, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennett DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, DeCarli C, Culebras A, Korczyn AD, Bogousslavsky J, Hartmann A, Scheinberg P. Vascular dementia: diagnostic criteria for research studies: report of the NINDSAIREN international workshop. Neurology. 1993;43:250-260. Bibliographic Links | [Context Link]

5. Wallin A, Blennow K. Heterogeneity of vascular dementia: mechanisms and subgroups. J Geriatr Psychiatry Neurol. 1993;6:177-188. Bibliographic Links | [Context Link]

6. Goodglass H, Kaplan E. The Assessment of Aphasia and Related Disorders. 2nd ed. Philadelphia, Pa: Lea & Febiger; 1983. [Context Link]

7. 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;2:189-198. [Context Link]

8. Mahoney FI, Barthel DW. Functional evaluation: Barthel Index. Md Med J. 1965;14:61-65. [Context Link]

9. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry. 1968;114:797-811. Bibliographic Links | [Context Link]

10. Tatemichi TK, Desmond DW, Paik M, Figueroa M, Gropen TI, Stern Y, Sano M, Remien R, Williams JBW, Mohr JP, Mayeux R. Clinical determinants of dementia related to stroke. Ann Neurol. 1993;33:568-575. Bibliographic Links | [Context Link]

11. Ginsberg MD, Hedley-Whyte ET, Richardson EP. Hypoxic-ischemic leukoencephalopathy in man. Arch Neurol. 1976;33:5-14. Bibliographic Links | [Context Link]

12. Brierley JB, Graham DI. Hypoxia and vascular disorders of the central nervous system. In: Adams JH, Corsellis JAN, Duchen LW, eds, Greenfield's Neuropathology. 4th ed. London, England: Edward Arnold; 1984:125-156. [Context Link]

13. Stern Y, Andrews H, Pittman J, Sano M, Tatemichi TK, Lantigua R, Mayeux R. Diagnosis of dementia in a heterogeneous population, part 1: development of a neuropsychological paradigm and quantified correction for education. Arch Neurol. 1992;49:453-460. Bibliographic Links | [Context Link]

14. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J Neurol Neurosurg Psychiatry. 1994;57:202-207. Bibliographic Links | [Context Link]

15. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry. 1983;46:5-8. Bibliographic Links | [Context Link]

16. Wade DT, Wood VA, Newer RL. Recovery after stroke: the first three months. J Neurol Neurosurg Psychiatry. 1985;48:7-13. Bibliographic Links | [Context Link]

17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987. [Context Link]

18. Hughes CP, Berg L, Danziger WL, Cohen LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566-572. Bibliographic Links | [Context Link]

19. Mayeux R, Pittman J, Andrews H, Denaro J, Palestroni A, Stern Y. Reliability and consistency in the diagnosis of Alzheimer's disease and related conditions in community-based studies. Neurology. 1993;42(suppl 2):A233. Abstract. [Context Link]

20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-481. [Context Link]

21. Cox DR. Regression models and lifetables. J R Stat Soc B. 1972;34:187-220. [Context Link]

22. Skoog I. Risk factors for vascular dementia: a review. Dementia. 1994;5:137-144. Bibliographic Links | [Context Link]

23. Sulkava R, Erkinjuntti T. Vascular dementia due to cardiac arrhythmias and systemic hypotension. Acta Neurol Scand. 1987;76:123-128. Bibliographic Links | [Context Link]

24. Brun A. Pathology and pathophysiology of cerebrovascular dementia: pure subgroups of obstructive and hypoperfusive etiology. Dementia. 1994;5:145-147. Bibliographic Links | [Context Link]

25. Mitchinson MJ. The hypotensive stroke. Lancet. 1980;1:244-246. [Context Link]

26. Cooper JK, Mungas D. Risk factor and behavioural differences between vascular and Alzheimer's dementias: the pathway to end-stage disease. J Geriatr Psychiatry Neurol. 1993;6:29-33. [Context Link]

27. Zhang WW, Badonic T, Hoog A, Jiang MH, Ma KC, Nie JX, Olsson Y, Sourander P. Structural and vasoactive factors influencing intracerebral arterioles in cases of vascular dementia and other cerebrovascular disease: a review. Dementia. 1994;5:153-162. [Context Link]

28. Harper SL. Effect of antihypertensive treatment on the cerebral microvasculature of spontaneously hypertensive rats. Stroke. 1987;18:450-456. Ovid Full Text | Bibliographic Links | [Context Link]

29. Irie K, Yamaguchi T, Minematsu K, Omae T. The J-curve phenomenon in stroke recurrence. Stroke. 1993;24:1844-1849. Ovid Full Text | Bibliographic Links | [Context Link]

30. Meyer JS, Judd BW, Tawakina T, Rogers RL, Mortel KF. Improved cognition after control of risk factors for multi-infarct dementia. JAMA. 1986;256:2203-2209. Bibliographic Links | [Context Link]

31. Nobili F, Rodriguez G, Marceno S, De Carli F, Gambaro M, Castello C, Pontremoli R, Rosadini G. Regional cerebral blood flow in chronic hypertension: a correlative study. Stroke. 1993;24:1148-1153. Ovid Full Text | Bibliographic Links | [Context Link]

32. Yao H, Sadoshima S, Ibayashi S, Kuwabara Y, Ichiya Y, Fujishima M. Leukoaraiosis and dementia in hypertensive patients. Stroke. 1992;23:1673-1677. Ovid Full Text | Bibliographic Links | [Context Link]

33. O'Brien MD. How does cerebrovascular disease cause dementia? Dementia. 1994;5:133-136. Bibliographic Links | [Context Link]

34. Jackson G, Pierscianowski TA, Mahon W, Condon J. Inappropriate antihypertensive therapy in the elderly. Lancet. 1976;2:1317-1318. Bibliographic Links | [Context Link]

35. Jansen PAF, Gribnau FWJ, Schulte BPM, Poels EFJ. Contribution of inappropriate treatment for hypertension to pathogenesis of stroke in the elderly. Br Med J. 1986;293:914-917. Bibliographic Links | [Context Link]

36. Cardiogenic dementia. Lancet. 1977;1:27-28. Editorial. [Context Link]

37. Sulg IA, Cronquist S, Schuller H, Ingvar DH. The effect of intracardial pacemaker therapy on cerebral blood flow and electroencephalogram in patients with complete atrioventricular block. Circulation. 1969;39:487-494. Abstract. [Context Link]

38. Rosenberg GA, Haaland KY. Cardiogenic dementia. Lancet. 1981;2:1171. Letter. [Context Link]

39. Volpe BT, Petito CK. Dementia with bilateral medial temporal lobe ischemia. Neurology. 1985;35:1793-1797. Bibliographic Links | [Context Link]

40. Shaw PJ, Bates D, Cartlidge NEF, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary bypass surgery. BMJ. 1985;291:1384-1387. [Context Link]

41. Hachinski VC. Preventable senility: a call for action against the vascular dementias. Lancet. 1992;340:645-648. Bibliographic Links | [Context Link]

IMAGE GALLERY

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	HI Disorder (n=34)	No HI Disorder (n=151)	P*
Age, y	69.9±8.7	70.4±7.5	.78
Education, y	11.1±4.3	10.3±4.8	.41
Sex, % male	47.1	48.3	.89
Race, % nonwhite	47.1	65.6	.04
Hypertension, % yes	67.7	75.5	.34
Diabetes, % yes	26.5	31.8	.54
Hypercholesterolemia, % yes	23.5	16.6	.34
Cardiac disease, % yes	64.7	41.1	.01
Cigarette smoking, % ever smoked	64.7	58.0	.47
Stroke location, %			
Cortical	61.8	48.3	.22
Subcortical	23.5	23.2	
Brain stem/cerebellum	14.7	28.5	
Stroke subtype, %			
Atherothrombotic	17.6	20.9	.28
Embolic	35.3	20.9	
Lacunar	20.6	32.4	
Cryptogenic	26.5	25.7	

*Based on *t* tests for continuous data and χ^2 analyses for categorical data.

Table 1

Pt	Age, y/Sex	Initial Stroke Location	MMSE Score†	Recurrent Stroke	HI Disorder
1	67/M	L parietal	26	Yes	Seizure
2	81/M	L parietal	18	No	Seizure
3	76/M	L frontal	13	No	Pneumonia
4	81/F	L cerebellar	22	No	Arrhythmia
5	88/F	R capsule	22	No	CHF
6	74/F	R frontal	26	Yes	Seizure
7	68/M	R parietal-occipital	18	Yes	CHF
8	79/M	L temporal-parietal	28	No	Pneumonia
9	91/M	L frontal	18	No	MI
10	88/F	R occipital	28	Yes	Sepsis
11	87/F	L basal ganglia-capsule	19	No	CHF
12	76/M	L temporal-parietal	27	No	CHF

Pt indicates patient; L, left; R, right; CHF, congestive heart failure; and MI, myocardial infarction.
†MMSE at 7 to 10 or 30 days after stroke (not used for the purpose of dementia diagnosis).

Table 2

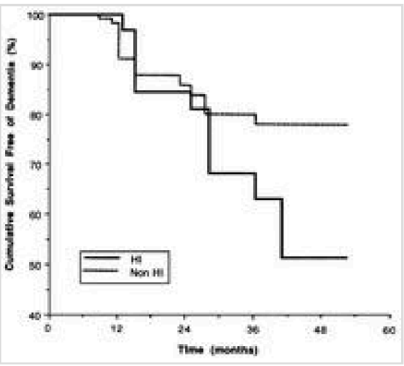

Figure 1

Variable	RR (95% CI) Model A	Model B
HI events (yes vs no)*	5.29 (2.52-11.11)	4.28 (1.92-9.55)
Age (vs 60-69 y)		
70-79 y	2.47 (1.10-5.52)	2.66 (1.17-6.06)
≥80 y	4.69 (1.64-13.44)	3.80 (1.25-11.60)
Education (vs ≥13 y)		
≤8 y	1.46 (0.56-3.82)	0.89 (0.31-2.57)
9-12 y	2.10 (0.75-5.86)	1.24 (0.39-3.89)
Sex (women vs men)	0.82 (0.40-1.67)	0.84 (0.39-1.80)
Race (white vs nonwhite)	0.44 (0.19-0.99)	0.47 (0.20-1.13)
Recurrent stroke (yes vs no)*		1.72 (0.72-4.11)
MMSE† (>24 vs ≤24)		3.55 (1.72-7.33)

*Time-dependent covariate.
†MMSE at 7 to 10 or 30 days after stroke (not used for the purpose of dementia diagnosis).

Table 3

Back to Top