Is Acute Alcohol Ingestion a Risk Factor for Ischemic Stroke?  
Results of a Controlled Study in Middle-Aged and Elderly Stroke Patients at Three Urban Medical Centers

Philip B. Gorelick, Miriam B. Rodin, Patricia Langenberg, Daniel B. Hier, John Costigan, Isabel Gomez, and Stephen Spontak

To assess the role of acute alcohol ingestion as a risk factor for cerebral infarction, we administered a pretested questionnaire to 205 middle-aged and elderly acute ischemic stroke patients and 410 outpatient controls matched by age, sex, race, and method of hospital payment. Paired Mantel-Haenszel analysis revealed that alcohol ingestion within 24 (p = 0.07) and 72 (p = 0.001) hours of stroke onset and medical histories of smoking (p < 0.0001), hypertension (p < 0.001), and transient ischemic attacks (p = 0.051) were more common among stroke index cases than controls. Matched multiple logistic analysis revealed that both hypertension (p < 0.05) and smoking (p < 0.05) were independently associated with stroke, while alcohol consumption was not. In analyses to assess the possibility of mutual confounding effects of independent variables, the effect of alcohol ingestion was lost when adjusting for smoking. We conclude that acute alcohol ingestion is not an independent risk factor for cerebral infarction in middle-aged and elderly patients. The apparent association between alcohol ingestion and ischemic stroke may be the result of the confounding effects of smoking. (Stroke 1987;18:359-364)

Prior studies from Finland,1-6 Denmark,7 the United States,8-11 Japan,12 and Yugoslavia13 suggest an association between alcohol intake and cerebral infarction or risk of death from stroke. Cerebral infarction has been reported following occasional ethanol intoxication or regular heavy drinking.2-4 Younger individuals appear to be at particularly high risk; however, a paucity of controlled data is available to assess the relation in older populations.14 The present study is a case-control study exploring the association between acute alcohol ingestion and ischemic stroke in predominantly black, middle-aged and elderly patients at 3 urban medical centers in Chicago, Ill.

Subjects and Methods  
Study Population

Two hundred and five consecutive acute ischemic stroke patients (index cases) hospitalized at the Michael Reese Hospital and Medical Center, the University of Illinois Hospital, and the Westside Veterans Administration Hospital between January 1, 1984, and January 1, 1985, were included in the study. Index cases were selected if they were 44 years of age or older, had experienced their first carotid or vertebrobasilar ischemic stroke, and had cranial computed tomography (CCT) consistent with acute cerebral infarction.15 CCT studies were reviewed by one of the principal investigators and a neuroradiologist before patient entry into the study. Patients were excluded if there was transient cerebral ischemia only, subarachnoid hemorrhage, intraparenchymal hemorrhage, nonatherosclerotic stroke,16 moderate or severe aphasia, or a moribund state. The diagnosis of cerebral infarction was based on the clinical and laboratory criteria of the NINCDS Stroke Data Bank. The study population included 43 patients (21%) with cerebral thrombosis, 31 (15%) with cerebral embolism, 48 (23%) with lacunar infarction, and 83 (41%) with infarction of unknown cause.

For each stroke index case 2 controls were selected from the general medicine outpatient clinic at each respective hospital. Index cases and controls were matched by age, sex, race, and method of hospital payment. There were 46 stroke index cases (22%) with private insurance, 69 (34%) with Medicare, 28 (14%) with public aid, and 62 (30%) with veteran status. Controls were selected by reviewing consecutive outpatient clinic records for any given appointment day; the first 2 outpatient records which could be appropriately matched to the index case were then selected. Because of the similarity in stroke populations,17 controls for the 80 stroke index cases from the Michael
Reese Hospital were selected from the general medicine outpatient clinic at the University of Illinois Hospital. All study participants signed consent forms in accordance with the requirements of individual hospital institutional review boards. Potential controls were excluded if they were relatives, close friends, or known drinking partners of stroke index cases.

Study Design

On admission to the hospital each stroke patient was examined by one of the principal investigators who validated the diagnosis of cerebral infarction. Stroke patients and controls who met the study inclusion criteria were then interviewed in person. Ninety-five percent were interviewed within 5 days of the index stroke and the remainder within 7–14 days. A pretested questionnaire was administered by investigators who were intensively trained in the use of the questionnaire, which contained items in nontechnical language designed to elicit history of known or potential risk factors for stroke and cardiovascular disease and history of usual alcohol consumption patterns. Specific items dealt with alcohol consumption for the period 24 and 72 hours preceding the index stroke, emphasizing day-of-the-week consumption,14 and past (≥ 1 year) and recent (<1 year) consumption. Included were questions pertaining to estimates of the frequency of weekday and weekend alcohol consumption, estimates of the amounts of beer, wine, hard liquor, and cordial or mixed drinks consumed, and history of feeling intoxicated or high following alcohol ingestion. Two parallel formats of the questionnaire, one for the stroke index cases and one for the controls, were designed. The informational content of the 2 questionnaires was identical; some differences in the wording was necessary so that the questions would be appropriately directed to a stroke index case or to a control subject.

Twenty-five stroke patients were excluded from the study as no direct history was available because of severe aphasia or coma or the patient refusing to participate in the study. Only 3 of the first 100 potential control patients refused to participate in the study. Validation of patient responses by interviewing spouses or close personal contacts was not performed.

The information from the patient questionnaires was transferred to a microcomputer data base system and then to an IBM mainframe computer for statistical analysis. Each questionnaire contained 98 items, making a total of 60,270 observations for the entire study.

Calculation of Absolute Ethanol Ingestion

The absolute amount of ethanol ingested was estimated according to the method of Klatsky et al. Numbers of reported servings were multiplied by estimated average serving size of that beverage and then by estimated average ethanol content of the beverage. Hard liquor was estimated at 1.5 ounces of 40% alcohol; beer at 12 ounces of 5% ethanol; and wine at 5 ounces of 12% ethanol. Mixed drinks and cordials were estimated as equivalent to 1 drink of hard liquor (see above). This yields a standard drink containing 0.6 ounces of pure ethanol.

Statistical Analysis

Univariate comparisons of cases and controls were performed using appropriate matched χ² and two-tailed t tests. Conditional (matched) logistic regression was used to calculate odds ratios to account for possible confounding factors. Because of the extreme right skew in the distribution, the mean values assumed by the logistic analysis could not be easily assessed by use of continuous values for absolute ethanol, log of absolute ethanol, pack-years of cigarettes, and log of pack-years of cigarettes. These data were reclassified using the median consumption of cases to generate qualitative independent variables for conditional logistic regression. Qualitative variables were also analyzed by unmatched logistic regression and the Mantel-Haenszel method for adjusted estimated relative risk. Tests for trend to identify dose–response relations were performed by the Mantel extension test. Both matched and unmatched continuous and qualitative analyses generated similar results. The qualitative unmatched Mantel-Haenszel analyses are presented for their simplicity of interpretation. Power calculations were set to detect a relative risk of 2.0, α = 0.05, β = 0.80, assuming 10% of controls and 20% of cases would have consumed alcohol in the 24 hours preceding stroke in the index case.

Results

Patient Characteristics

Stroke index cases were more likely to have a past medical history of either hypertension (p < 0.001) or transient ischemic attacks (TIA) (p = 0.051), whereas control subjects were more likely to have a past medical history of limb claudication (p = 0.051) or hypercholesterolemia (p < 0.001) (Table 1). The number of subjects in the latter 2 risk categories was small, and the results may have reflected an artifact in the data or a selection bias when choosing controls. The number of subjects with TIA was also small and could not be accommodated in subsequent regression and stratified analyses. No significant differences were reported in prior history of myocardial infarction, angina pectoris, cardiac arrhythmias, and diabetes mellitus among cases and controls (Table 1).

Current and Past Alcohol Consumption

Stroke index cases and controls did not differ significantly in the proportion of current drinkers; approximately 65% of index cases and 56% of controls reported having had at least 1 drink in the past year (Table 2). About 25% of index cases compared with 29% of controls reported that they had been former drinkers (consumption of at least 1 drink in their lifetime but none in the past year). About 9% of index cases and 15% of controls reported life-long abstinence (Table 2). Among current drinkers only, approximately 24 and 16% of respective index cases and controls reported drinking within 24 hours of the index stroke, with about a 1¾ ounce difference (about 2 drinks) in absolute ethanol consumed (Table 2). About 10% more index cases than controls drank within 3...
days of the index stroke, with index cases consuming 35% (about 1.3 ounces) more than controls (Table 2).

While mean alcohol consumption levels for current drinkers only did not differ significantly among index cases and controls within 24 and 72 hours of the index stroke, when all index cases and controls were considered there was a significantly higher proportion of index cases (p = 0.001) than controls consuming alcohol within 72 hours of the index stroke. No significant difference, however, was noted among index cases and controls for alcohol consumption within 24 hours of the index stroke. No significant difference was detected between index cases and controls consuming alcohol within 24 hours of the index stroke (p = 0.001) than controls consuming alcohol within 24 or 72 hours.

Subsequent analyses showed no specific temporal day-of-the-week pattern in alcohol consumption or stroke occurrence. This may reflect the nature of our study population, largely elderly and unemployed or retired, and thus not constrained in their drinking patterns by work demands.

An unpaired analysis comparing index cases and controls was performed to determine if there was a threshold of alcohol consumption at which cerebral infarction occurred more frequently. When alcohol consumption thresholds were set at progressively higher levels up to 3.5 ounces of absolute ethanol, no significant threshold effect was observed.

Analysis of day-of-the-week alcohol consumption was performed to determine if there was a possible confounding effect of temporal patterns of drinking associated with workday versus weekend drinking. Subsequent analyses showed no specific temporal day-of-the-week pattern in alcohol consumption or stroke occurrence. This may reflect the nature of our study population, largely elderly and unemployed or retired, and thus not constrained in their drinking patterns by work demands.

Table 2. Current and Past Alcohol Consumption

<table>
<thead>
<tr>
<th>Stroke cases (n = 205)</th>
<th>Controls (n = 410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current drinker*</td>
<td>65.3%</td>
</tr>
<tr>
<td>Former drinker†</td>
<td>25.3%</td>
</tr>
<tr>
<td>Never drank</td>
<td>9.4%</td>
</tr>
<tr>
<td>Alcohol consumption within 24 hours of index stroke‡</td>
<td>23.6%</td>
</tr>
<tr>
<td>Alcohol consumption within 72 hours of index stroke§</td>
<td>33.9%</td>
</tr>
<tr>
<td>Alcohol consumption within 24 hours of index stroke§</td>
<td>4.01 ± 4.4</td>
</tr>
<tr>
<td>Alcohol consumption within 72 hours of index stroke§</td>
<td>(0.72-20.80)</td>
</tr>
</tbody>
</table>

Data are percent for the first 5 classifications, mean ± SD (range in parentheses) ounces of absolute ethanol for alcohol consumption within 24 or 72 hours.

*Current drinker includes those who have consumed at least 1 drink in the past year.
†Former drinker includes those who have consumed at least 1 drink in their lifetime but have not drank in the past year.
‡Percent based on ratio of current drinkers consuming alcohol within 24 or 72 hours of index stroke and total number of current drinkers.
§Calculation based on only those who consumed alcohol within 24 or 72 hours of index stroke.

Table 3. 24-Hour Stratified Ethanol Intake and Stroke

<table>
<thead>
<tr>
<th>Absolute ounces of ethanol consumed</th>
<th>Stroke cases % (No.)</th>
<th>Controls % (No.)</th>
<th>Unadjusted odds ratios*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76.4 (155)</td>
<td>83.7 (340)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;0,≤2.4</td>
<td>10.8 (22)</td>
<td>8.9 (36)</td>
<td>1.33</td>
</tr>
<tr>
<td>&gt;2.4</td>
<td>12.8 (26)</td>
<td>7.4 (30)</td>
<td>1.89</td>
</tr>
</tbody>
</table>

χ² = 5.782, df = 2, p = 0.056.
*Mantel extension test for trend in odds ratios = 5.755, df = 1, p = 0.016.

Gorelick et al  Alcohol as Risk Factor for Stroke
Current and Past History of Smoking

Over 59% of stroke index cases were current cigarette smokers (smoked within the past year); 19.0% were former cigarette smokers, and 21.5% never smoked (Table 4). Of controls, 30.1% were current cigarette smokers, 38.8% former cigarette smokers, and 31.0% never smoked (Table 4). Stroke index cases were more likely to have been current cigarette smokers (p < 0.0001), to have smoked within 24 hours of the index stroke (p < 0.0001), and to have a significantly higher number of mean pack-years exposure (p = 0.0001) than controls (Table 4). The Mantel-Haenszel test of association between smoking and stroke stratified on the median of the cases' cigarette exposure (33 pack-years) showed a powerful association and a highly significant dose-response effect (Table 5). When the analysis was performed for age-specific groups (<65 and ≥ 65 years of age), the results were similar.

Influence of Confounding Factors on the Association of Alcohol Consumption and Stroke

To assess the role of known or potential risk factors for stroke as confounding factors, the independent variables alcohol, smoking, and hypertension were analyzed by both Mantel-Haenszel and matched multiple logistic techniques. By both methods the results were similar. Table 6 summarizes the results of the matched multiple logistic model for 24-hour alcohol consumption. Both hypertension (p < 0.05) and smoking (p < 0.05) were independently associated with stroke; 24-hour alcohol consumption was not. The results of a parallel analysis evaluating hypertension, smoking, and 72-hour alcohol consumption were similar.

By the Mantel-Haenszel technique, hypertension was found to be a risk factor for ischemic stroke that was independent of alcohol ingestion. After controlling for smoking, no association between alcohol ingestion and ischemic stroke was found. These relations held true for both 24- and 72-hour alcohol ingestion. When the independent variables smoking and hypertension were analyzed for confounding effects, smoking and hypertension emerged as strong independent predictors of ischemic stroke, whereas the effect of alcohol ingestion was lost after controlling for smoking. Thus, the apparent association between alcohol consumption and stroke may simply reflect the association of alcohol with smoking.

Discussion

Several clinical studies have suggested that alcohol consumption is related to stroke. In uncontrolled case series, Pakkenberg and Balow et al have proposed that alcohol ingestion may predispose to thromboembolic stroke, especially in young adults. In an autopsy study Walbran and colleagues reported cerebral infarction more commonly at an earlier age in alcoholics than in nonalcoholics. In a controlled retrospective study examining the association between alcoholism and thrombosis in normotensive patients <50 years of age, Lee found that histories of excessive alcohol intake were more frequent in stroke index cases than controls. Data from the Framingham Study also suggest an association between alcohol intake and the incidence of stroke in general and brain infarction, but only in men. The Honolulu Heart Study showed that alcohol consumption was associated with intracranial hemorrhage but not thromboembolic strokes. These relations remained significant after controlling for the effects of hypertension. Several other studies have reported alcohol as a risk factor for fatal or nonfatal hemorrhagic stroke, especially subarachnoid hemorrhage. The subsequent risk of intracranial hemorrhage may be decreased, however, by reduction of alcohol intake.

In more recent studies Taylor and Coombs-Orme linked acute heavy alcohol consumption with stroke

<table>
<thead>
<tr>
<th>Table 4. Current and Past Cigarette Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke cases (n = 205)</td>
</tr>
<tr>
<td>Controls (n = 410)</td>
</tr>
<tr>
<td>Current cigarette smoker*</td>
</tr>
<tr>
<td>Former cigarette smoker</td>
</tr>
<tr>
<td>Never smoked</td>
</tr>
<tr>
<td>Smoking within 24 hours of index stroke*</td>
</tr>
<tr>
<td>Cigarette smoking†</td>
</tr>
</tbody>
</table>

Data are percent for the first 4 categories, mean ± SD (range in parentheses) in pack-years for cigarette smoking. Smoking within 24 hours includes cigarettes, pipes, and cigars.

*Groups differ, p < 0.0001, χ² test, df = 1.
†Means differ, p = 0.0001, two-tailed t test.

<table>
<thead>
<tr>
<th>Table 5. Association Between Cigarette Smoking and Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack-years Stroke cases Controls Unadjusted odds ratios*</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>&gt;0,≤33</td>
</tr>
<tr>
<td>&gt;33</td>
</tr>
</tbody>
</table>

χ² = 57.035, df = 2, p < 0.001.
*Mantel extension test for trend = 56.848, df = 1, p < 0.001.

<table>
<thead>
<tr>
<th>Table 6. Matched Logistic Model of Association Between 24-Hour Alcohol Intake, Cigarette Smoking, Hypertension, and Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variable</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>24-Hour alcohol consumption</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>History of hypertension</td>
</tr>
</tbody>
</table>

24-hour alcohol entered as 0, > 0 but ≤ 2.4, or > 2.4 ounces; cigarette smoking entered as 0, > 0 but ≤ 33, or > 33 pack-years; hypertension entered as present or absent.

ψ represents the odds ratio of level i to level 1 (baseline) of the variable, adjusted for all other variables.

* p < 0.05.
among young adults. In case series from Finland, Hillbom and Kaste\textsuperscript{2-4} reported an increase in the risk of ischemic brain infarction in young adults and adolescents with occasional ethanol intoxication, and in middle-aged women and young men with both occasional alcohol intoxication and regular heavy drinking. The latter studies\textsuperscript{2-4} have been criticized because select populations of hospitalized patients were compared with the general Finnish population from a different time period, and ascertainment of data on alcohol consumption was different in cases and controls.\textsuperscript{14}

Our results do not support a hypothesized role for acute alcohol ingestion as an independent risk factor for ischemic stroke. Although a borderline association of acute alcohol ingestion within 24 and 72 hours of stroke was noted after adjusting for hypertension, the effect was lost when controlling for smoking, suggesting that the association between acute alcohol intake and ischemic stroke was largely due to the confounding effect of smoking. In our study population hypertension and smoking were found to be independent risk factors for cerebral infarction.

Although our study suggests that acute alcohol ingestion is not an independent risk factor for ischemic stroke in middle-aged and elderly patients, such a relation may hold true for young adults.\textsuperscript{2-4} This may reflect differences in risk factors for ischemic stroke among the young compared with the middle-aged and elderly. The stronger effects of hypertension and smoking in older subjects may prevent detection of any effect referable to alcohol. In younger subjects, in whom the atherosclerotic process is not as far advanced, carefully controlled studies with the evaluation of potential confounding factors might ultimately support such an association.\textsuperscript{11,14} Recent clinical studies suggest several mechanisms by which alcohol ingestion might contribute to stroke. These include 1) induction of cardiac arrhythmias and cardiac wall motion abnormalities that predispose to cerebral embolism,\textsuperscript{26-31} 2) induction of hypertension,\textsuperscript{32-35} 3) enhancement of platelet aggregation and activation of the clotting cascade,\textsuperscript{36-38} and 4) reduction of cerebral blood flow by stimulation of cerebral vascular smooth muscle contraction or by altering cerebral metabolism.\textsuperscript{39-41} Additionally, the choice of alcoholic beverage and the propensity to extreme alcohol intake\textsuperscript{2-4} might also influence the risk of ischemic stroke in specific patient populations. In our study only 31% of stroke index cases and 17% of controls who drank within 24 hours of the index stroke reported subjective intoxication, suggesting high peak blood alcohol levels. Blood alcohol levels were not determined in any of our patients within hours of alcohol ingestion, however, making quantitative correlation of blood alcohol level and stroke occurrence impossible. Correlation of alcoholic beverage type and stroke occurrence could not be performed due to the small numbers of subjects enrolled in the study who drank within 24 and 72 hours of the index stroke.

Negative findings in a case-control study should direct attention to potential sources of bias and confounding. We believe that such factors probably did not play a significant role in our study. First, index cases and controls were matched on the principal correlates of alcohol consumption: age, sex, and social class.\textsuperscript{42} Failure to match on these variables could lead to spurious associations, most likely in the direction of strong inverse associations between alcohol intake and stroke. Second, the use of outpatient controls rather than community controls raises the possibility of a selection bias toward higher risk in the former group since outpatient controls are a select group and not representative of the community. While analysis of confounding factors indicated that our index cases and controls were indeed dissimilar, some unexpected findings were noted. For example, 2 of the confounding factors, limb claudication and hypercholesterolemia, occurred at a higher frequency among controls. While the numbers were small enough that further controlled analysis would not have changed our conclusions, different results for the distribution of these factors might have been obtained had it been possible to select controls from the general population. Perhaps the greatest weakness of our study was the use of self-report for alcohol and cigarette exposure and risk factor determination. Alcohol and cigarette exposure can only be ascertained by direct inquiry. We believe that recall bias did not significantly influence our findings for alcohol exposure as our results were consistent with larger prospective surveys of drinking among the elderly.\textsuperscript{43-44} Nevertheless, misclassification of risk factors due to generally poor recall or poor level of medical care must be considered in a largely innercity study population. Finally, it is possible that a survivorship cohort effect influenced our results; that is, in younger age groups the effect of alcohol was so potent that persons at risk had died prior to enrollment in the study. A secondary analysis of our data stratified on the basis of age (< or >60 years) revealed no age-related cohort effect. Nonetheless, none of our subjects was <40 years of age, and selective survival beyond the age of 40 might exist.

Addendum. Since the submission of our article, Gill and colleagues\textsuperscript{45} have reported that heavy current alcohol intake is an independent risk factor for stroke in men.

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