Recent Heavy Drinking of Alcohol and Embolic Stroke
Matti Hillbom, MD, PhD; Heikki Numminen, MD; Seppo Juvela, MD, PhD

Background and Purpose—Epidemiological evidence suggests that heavy alcohol consumption increases the risk for ischemic stroke, whereas light-to-moderate alcohol intake decreases the risk, but the role of different drinking patterns has remained unclear. We investigated recent light, moderate, and heavy alcohol drinking and former heavy drinking as risk factors for acute ischemic brain infarction by etiological subtype of stroke.

Methods—We compared 212 consecutive patients aged between 16 and 60 years, who were completely evaluated for the etiology of their ischemic stroke, with 274 control subjects admitted to the emergency unit of the same hospital. ORs, as estimates of multivariate relative risks (RRs), and 95% CIs after adjustment for possible confounding variables were calculated by logistic regression. The ORs were adjusted for age, sex, body mass index, hypertension, diabetes, hyperlipemia, current smoking, and history of migraine.

Results—Recent heavy drinking but not former heavy drinking was an independent risk factor for stroke (RR 1.82, 95% CI 1.08 to 3.05). Consumption of 151 to 300 g and >300 g alcohol within the week preceding the onset of stroke significantly increased the risk for cardioembolic and cryptogenic stroke. Consumption of >40 g alcohol within the preceding 24 hours increased the risk for cardiogenic embolism to the brain among those who had a high-risk source (RR 4.75, 95% CI 1.23 to 18.4), the risk for tandem embolism among those who had prominent large-artery atherosclerosis (RR 7.68, 95% CI 1.82 to 32.3), and the risk for cryptogenic stroke (RR 3.84, 95% CI 1.69 to 8.71). Light drinking did not increase the risk for stroke.

Conclusions—We conclude that acute drinking of intoxicating amounts of alcohol may trigger the onset of embolic stroke among subjects who have a source of thrombus in the heart or the large arteries. (Stroke. 1999;30:2307-2312.)

Key Words: alcohol drinking ■ cardioembolic stroke ■ cerebral infarction ■ risk factors

The role of alcohol consumption as an independent risk factor for ischemic brain infarction has remained unclear. Both mortality and morbidity from ischemic brain infarction seem to be increased among heavy alcohol drinkers. A synergistic effect of alcohol consumption and hypertension on the risk of ischemic stroke has been observed. Several investigators report a protective effect of light or moderate drinking, but others claim that there is no convincing evidence to support such an effect. It has been pointed out that control for confounding factors as well as analyses of the characteristics of abstainers are lacking in most studies.

Few studies have taken into account different drinking patterns. However, one cohort study indicated significant associations between ischemic stroke mortality and drinking habits. Compared with lifelong abstainers, men who reported that they often or sometimes felt intoxicated and men who reported binge drinking had a greater risk of dying from ischemic stroke. A case-control study showed that heavy alcohol ingestion within the 24 hours preceding the onset of stroke was not a risk factor for ischemic brain infarction, whereas another found that it was.

Of particular interest is the observation that heavy drinking results in an increased rate of ischemic stroke recurrences. In the Northern Manhattan Stroke Study, nearly half of those with a history of heavy alcohol use had a recurrent brain infarction within 5 years compared with 22% of those without heavy alcohol use. It is possible that recent heavy drinking and even occasional drinking for intoxication could trigger an ischemic stroke. Cardioembolic stroke in particular could well be precipitated by binge drinking, because alcoholic intoxication may precipitate untoward effects on circulation and cardiac rhythm. We lack studies of alcohol drinking patterns in relation to the onset of different subtypes of ischemic stroke.

The aim of the present study was to demonstrate the role of different drinking patterns in relation to risk of ischemic stroke subtype. We investigated strokes due to cardiogenic emboli, large-artery atherosclerosis (tandem emboli), and cervicocerebral arterial dissection, as well as strokes of unknown origin (cryptogenic stroke). The role of former heavy drinking was also evaluated. We found an association with recent heavy (and moderate) drinking for brain infarct-
tion and particularly with recent heavy drinking for cardio-
genic and cryptogenic brain embolism.

Subjects and Methods

The study population consisted of 212 patients (54 females and 158 males aged 16 to 60 years) with first-ever acute brain infarction who were admitted on an emergency basis to the Helsinki University Central Hospital and 274 control subjects (112 females and 162 males aged 16 to 67 years) from the same hospital who were matched with the brain infarction patients by age, day of onset of symptoms, and acuteness of disease onset. The control subjects were admitted to the emergency department because of acute appendicitis (n=122), nephrolithiasis (n=63), dyspnea (n=42), viral meningitis (n=25), and cholecystitis (n=22). According to the literature, none of these medical emergencies are considered to accumulate among heavy drinkers or teetotalers. These control subjects have previously been validated to be representative of the general population of the catchment area of our hospital by sex, age, recent alcohol drinking, and smoking habits.15–17 The study protocol was approved by the institutional ethics committee, and informed consent was obtained before interviewing the patients. The data and permission for the study were given by a relative if the patient was too ill to cooperate. None of the case subjects, relatives, or controls refused to participate.

All the patients had definite clinical signs and symptoms of acute brain infarction on admission. Patients who were incompletely evaluated for the etiology of stroke were excluded. We also excluded the subjects with acute brain infarction precipitated during surgery or angiography and those with vasculitides, blood dyscrasias, and illicit drug use. We finally had a total of 216 patients, who could be classified into the following 7 categories, the diagnostic criteria of which have been reported previously18: (1) large-artery atherosclerosis, (2) cardioembolism with a high-risk source, (3) cardioembo-
lism with a medium-risk source, (4) small-artery occlusion (lacune), (5) stroke of other determined etiology, (6) stroke with ≥2 causas identified, and (7) cryptogenic stroke. We further excluded 4 patients belonging to category 6 (≥2 causes), and the remaining 212 patients consisted of 76 with cardioembolism (38 with a high-risk source), 68 with a negative evaluation (cryptogenic stroke), 34 with large-artery atherosclerosis, 24 with cervicocephalic arterial dissection, and 10 with small-artery occlusion.

The protocol applied to the etiological assessment of the present patient series was basically as follows. The first step included routine laboratory tests and ECGs and differentiated between hemorrhagic and ischemic strokes on the basis of CT of the head performed on each individual within 24 hours of the onset of stroke. The second step included duplex imaging of the carotid and vertebral arteries and/or an aortic arch angiogram obtained with the intra-arterial digital subtraction technique, and these investigations were made during the first week after the onset of stroke. The third step took place at the end of the first week and included cardiac imaging by transesophageal and/or transthoracic echocardiography. Finally, if these steps did not reveal the precise etiology of the index stroke, special laboratory tests were tailored to establish the rare hematolog-
ical and other abnormalities possibly predisposing to stroke. This protocol made it possible to classify the patients into etiological categories of acute ischemic stroke.

The patients and the control subjects were personally interviewed according to a structured questionnaire. There were no differences in the interview times and environments between the control and case patients. The questionnaire included questions about the exact time of disease onset; the subject’s height and weight; previous diseases and hospital visits; recent drug use, including illicit drugs; recent and previous drinking of alcohol; and current and previous smoking status. Recent drinking was estimated by asking the patient or control subject how many drinks of alcohol (with 12 g of ethanol considered a standard drink) they had consumed during the 24 hours preceding the onset of the first symptoms of stroke. The category of heavy drinkers included subjects whose recent mean weekly alcohol intake had regularly exceeded 300 g of ethanol, or who were classified as problem drinkers by using the short CAGE questionnaire.19 Accord-

| TABLE 1. Baseline Characteristics in 212 Patients with Acute Brain Infarction and 274 Control Subjects |
|--------------------------------------------------|--------------------------------------------------|
| Characteristic                                      | Case (%)                                    | Control (%)                                 |
| No. of patients                                      | 212                                          | 274                                          |
| Sex (male/female)                                    | 158/55                                       | 162/112                                      |
| Mean±SD age, y                                      | 44±10                                        | 44±13                                        |
| Mean±SD body mass index, kg/m²                       | 26±4                                         | 26±4                                         |
| Hypertension (%)                                    | 82 (39)                                      | 55 (20)                                      |
| Diabetes mellitus (%)                               | 23 (11)                                      | 18 (7)                                       |
| Hyperlipemia (%)                                    | 35 (17)                                      | 24 (9)                                       |
| Migraine (%)                                         | 32 (15)                                      | 43 (16)                                      |
| Current smoking (%)                                 | 113 (53)                                     | 100 (36)                                     |
| Heavy and/or problem drinking (%)                   | 62 (29)                                      | 44 (16)                                      |
| Former heavy drinking (%)                           | 23 (11)                                      | 32 (12)                                      |
| Recent alcohol consumption (%)                      |                                              |                                              |
| Within 24 h                                         |                                              |                                              |
| 0 g                                                  | 94 (44)                                      | 195 (71)                                     |
| 1–40 g                                               | 36 (17)                                      | 58 (21)                                      |
| >40 g                                                | 49 (23)                                      | 21 (8)                                       |
| Within 1 wk                                         |                                              |                                              |
| 0 g                                                  | 54 (25)                                      | 118 (43)                                     |
| 1–150 g                                              | 68 (32)                                      | 128 (47)                                     |
| 151–300 g                                            | 29 (14)                                      | 16 (6)                                       |
| >300 g                                               | 28 (13)                                      | 12 (4)                                       |

Values given are number of patients unless otherwise stated.

ingly, heavy drinkers included both recent heavy drinkers and former heavy drinkers. Former heavy drinkers were separated from the group of heavy drinkers by their report of no alcohol intake during the week preceding the index admission.

The smokers were categorized into current cigarette smokers and nonsmokers. The latter included former regular cigarette smokers who had quit a year or more previously. The body mass index, calculated as weight in kilograms/height in meters$^2$, was used as the index of relative weight. The subjects were considered hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/95 mm Hg or if they were taking antihypertensive medication. The categories of diabetics and hyperlipemics included subjects with previously diagnosed diabetes or hyperlipemia treated either by drugs or diet. Migraine was defined as a typical migrainous headache with or without aura in the patient’s earlier history or immediately preceding the onset of brain infarction.

The data were analyzed with biomedical data package statistical software (1993 version by BMDP Statistical Software Inc). The categorical variables were compared using the Fisher exact 2-tailed test or the Pearson chi$^2$ test. ORs, as estimates of multivariate relative risks (RRs), and 95% CIs before and after adjustment for possible confounding variables were calculated by logistic regression. Hypotheses were tested and 95% CIs determined using standard error estimates for the logistic coefficients.

Results

Current smoking and heavy drinking were common characteristics of the stroke patients (Table 1), but the patient group did not differ markedly from the control group by the number of former heavy drinkers or subjects with a history of migraine. Hypertension, diabetes, and hyperlipemia were more frequent among the stroke patients than the control subjects, as expected.
Multiple stepwise logistic regression showed that hypertension, current smoking, and heavy drinking significantly increased the risk for ischemic brain infarction (Table 2). Hyperlipemia, history of migraine, and diabetes also tended to increase the risk, but obesity did not.

Because there could be an interaction between alcohol drinking and hypertension, simultaneous inclusion of both in the model may decrease the significance of each as a risk factor. This was not the case, however, because the omission of hypertension from the model did not change the association between heavy drinking and ischemic brain infarction (adjusted RR 1.83, 95% CI 1.10 to 3.03). If heavy drinking was replaced by former heavy drinking in the model, former heavy drinking did not increase the risk for brain infarction (adjusted RR 0.79, 95% CI 0.41 to 1.55).

We also tested the role of recent heavy drinking by including the consumption of alcohol within the 24 hours or the week preceding the onset of illness in the model as the drinking parameter. Moderate (151 through 300 g) and heavy (>300 g) alcohol intake during the preceding week significantly (P<0.001) increased the risk of brain infarction. The adjusted RRs were 3.61 (95% CI 1.67 to 7.79) and 3.74 (95% CI 1.61 to 8.72), respectively. Similar RRs (3.42 and 4.04, respectively) were found after the omission of hypertension from the model. Recent light drinking (1 through 40 g) within the preceding 24 hours before the onset of stroke did not increase the risk, but recent heavy drinking (>40 g) showed a significantly elevated RR of 4.19 (95% CI 2.24 to 7.81). Again, the omission of hypertension from the model did not markedly influence the risk caused by recent alcohol intake.

Next, we tested which factors increased the risk for cardiogenic brain embolism. Heavy drinking was the most significant risk factor (adjusted RR 0.92, 95% CI 0.20 to 4.22), whereas recent heavy drinking was. The adjusted RRs for brain infarction by heavy alcohol intake within 24 hours and 1 week before the onset of stroke were 4.75 (95% CI 1.23 to 18.4) and 14.5 (95% CI 2.12 to 99.2), respectively. Even moderate (151 through 300 g) alcohol intake within the preceding week seemed to increase the risk (adjusted RR 19.7, 95% CI 2.19 to 177.0).

In the group of patients with stroke due to cardioembolism with a medium-risk source, hyperlipemia (adjusted RR 4.05, 95% CI 1.31 to 12.6) and heavy drinking (adjusted RR 2.46, 95% CI 1.01 to 5.99) were the only significant (P<0.05) risk factors for brain infarction. However, heavy alcohol intake within either the preceding 24 hours or 1 week before the onset of stroke was not a risk factor of statistical significance.

Hypertension (adjusted RR 2.31, 95% CI 1.07 to 4.99) and a history of migraine (adjusted RR 2.09, 95% CI 1.03 to 4.23) were significant risk factors for cryptogenic stroke (Table 4). Recent heavy drinking either within the preceding week (adjusted RR 4.68, 95% CI 1.51 to 14.5) or within the preceding 24 hours (adjusted RR 3.84, 95% CI 1.69 to 8.71) was also a significant (P<0.01) risk factor, whereas former heavy drinking was not (adjusted RR 0.83, 95% CI 0.32 to 2.16).

As expected, current smoking was a significant (P<0.05) risk factor for large-artery atherosclerotic brain infarction (Table 5). Former heavy drinking was not a risk factor (RR 0.48, 95% CI 0.10 to 2.25), but, unexpectedly, heavy drinking within the preceding 24 hours significantly (P<0.001) increased the risk (RR 7.68, 95% CI 1.82 to 32.3), even after adjustment for potential confounding factors.
Table 5. Multivariate RRs of Large-Artery Atherosclerotic Brain Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>3.34*</td>
<td>1.08–10.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.68</td>
<td>0.81–8.87</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.09</td>
<td>0.47–9.31</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>2.01</td>
<td>0.66–6.07</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>2.01</td>
<td>0.55–7.39</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.27</td>
<td>0.03–2.67</td>
</tr>
</tbody>
</table>

RRs represent comparisons with patients without a risk factor and have been adjusted for age, sex, body mass index, and the other variables listed in the table.

*P<0.05.

In the group of patients with cervicocerebral arterial dissection, male sex (adjusted RR 5.31, 95% CI 1.08 to 26.1) and heavy drinking within the preceding 24 hours before the onset of stroke (adjusted RR 3.67, 95% CI 0.97 to 13.8) increased the risk for brain infarction. Cases with small-artery occlusion (lacune) were too few for a meaningful analysis.

We also performed gender-specific analyses of the material. After the omission of women from the model, higher RRs for brain infarction were observed in men (than in men and women together) by alcohol intake within 24 hours (>40 g; 4.78, 95% CI 2.31 to 9.86) and 1 week (>300 g; 4.24, 95% CI 1.63 to 11.0), respectively. The adjusted RRs caused by recent heavy drinking were not statistically significant for women. For example, the recent week (>200 g) and 24-hour (>40 g) alcohol intake in women resulted in RRs of 1.87 (95% CI 0.31 to 11.4) and 1.78 (95% CI 0.38 to 8.35), respectively. For cardiogenic brain embolism in men, the adjusted RRs caused by recent moderate (151 through 300 g) and heavy (>300 g) alcohol intake were 9.39 (95% CI 2.10 to 42.0, P<0.01) and 7.47 (95% CI 1.75 to 31.9), respectively. The adjusted RR for cardiogenic brain embolism by heavy (>40 g) alcohol intake within 24 hours before the onset of stroke was 4.57 (95% CI 1.11 to 18.9) in men.

Discussion

The risk factors for ischemic brain infarction differ by subtype of stroke. We found recent heavy drinking of alcohol to increase the risk of cardioembolic stroke, whereas former heavy drinking and recent light drinking did not. Alcohol intake within 24 hours (>40 g) and 1 week (>300 g) before the onset of stroke were both found to be significant and independent risk factors for cardioembolic stroke in men. Significant risks were not observed in women, because the material was too small and women rarely drink for intoxication in Finland.

Previous case-control studies have not shown recent heavy alcohol intake to be a risk factor for cardioembolic stroke. Atrial fibrillation is a common cause of embolic stroke, and the frequency of atrial fibrillation increases by age. However, alcohol has not been found to be a risk factor for brain infarction in elderly people, possibly because they often have other causes of stroke, such as cerebrovascular atherosclerosis, and because they seldom drink for intoxication. In studies in which recent alcohol intake was not found to be a risk factor for brain infarction, the number of subjects who had consumed intoxicating amounts of alcohol during the week preceding the onset of stroke was very small, and the association did not reach statistical significance or the cases of cardiogenic brain embolism were excluded or were too few to allow meaningful statistical analysis. Because of the limited therapeutic options, patients are relatively seldom thoroughly evaluated for all the possible sources of cardiogenic brain embolism.

Alcohol may account for a third of the new cases of atrial fibrillation, and atrial fibrillation may occur with acute and chronic alcohol ingestion. Cardiac arrhythmias are commonly associated with alcoholic cardiomyopathy, and we had some cases of alcoholic cardiomyopathy in our series. We also found cases with previous myocardial infarction concurrent with atrial fibrillation, cardiac insufficiency, and heart dilation.

Some bias may be caused by subjects having more than one possible etiology for the stroke, but we excluded such cases from our series (4 patients with a potential cardiac source of embolism who also had severe cervical carotid stenosis ipsilateral to the stroke). Bias may also be caused by erratic reporting of recent alcohol intake. Patients admitted to the emergency ward of a general hospital tend to underestimate rather than overestimate their recent alcohol consumption. Accordingly, the subjects in our series may have consumed larger amounts of alcohol than they reported. If this is true, the significance of our observation could be even greater than observed.

In subjects with a high-risk source of cardiogenic brain embolism, hypertension was the most significant risk factor for stroke, but recent heavy alcohol intake was another important and independent risk factor. We identified atrial fibrillation, recent myocardial infarction together with an akinetic or hypokinetic left ventricular segment, dilated cardiomyopathy, and a left atrial appendage thrombus as high-risk sources of cardioembolism in these subjects. The tendency of alcohol to increase the stroke risk was also observed in patients with a medium-risk source of cardioembolism (eg, patent foramen ovale), but it was weaker.

Our observations indicate that recent heavy drinking of alcohol may trigger cardiogenic brain embolism. There are several plausible mechanisms that could explain the effect. First, heavy drinking of alcohol precipitates cardiac arrhythmias. The propagation of thrombi is certainly enhanced by cardiac arrhythmias, and alcohol, even in modest doses, has the potential to produce arrhythmias in patients with a history of chronic alcohol consumption and heart disease. It is also conceivable that some subjects may show genetically greater sensitivity to the arrhythmogenic effects of alcohol than others. The case report of a 37-year-old man prone to atrial flutter, who sustained 2 separate ischemic strokes during acute alcoholic intoxication, suggests that cardiac arrhythmias, even in the absence of overt cardiomyopathy and coronary heart disease, could precipitate cardiogenic brain embolism. An experimental study demonstrated that subjects prone to alcohol-induced atrial fibrillation seem to develop an exaggerated sympathetic reaction during even a
modest (blood alcohol 1.5/1000) acute alcoholic intoxication.\textsuperscript{20}

Second, alcohol and possibly also acetaldehyde seem to be cardiotoxic agents that cause alcoholic cardiomyopathy. This disease, which is diagnosed upon the presence of heavy drinking, and amelioration after prolonged abstinence presents a broad spectrum of cardiac abnormalities, whose significance as risk factors for thrombus formation has not been thoroughly investigated. There are case reports\textsuperscript{31} which demonstrate that alcoholic cardiomyopathy results in cardiogenic brain embolism.

Third, alcohol ingestion may aggravate sleep apneas in subjects with sleep apnea syndromes. Sleep apnea syndromes are characterized by repeated long apneic episodes, arterial hypoxia, cardiac dysfunction, and arrhythmias. The arrhythmias may predispose to the formation of intracardiac thrombi and also dispatch existing thrombi into circulation.

Finally, the syndrome of acute alcohol withdrawal and troublesome hangover may result in vomiting causing a spontaneous Valsalva maneuver, which facilitates the entrance of paradoxical emboli via atrial septal defects and patent foramen ovale into the cerebral circulation.

We also observed that heavy alcohol intake within 24 hours before the onset of stroke was a risk factor for stroke due to large-artery atherosclerosis. This unexpected finding could possibly be explained by the effect of acute severe alcoholic intoxication on circulation. A local thrombus attached to the arterial wall may be easily dislodged by a sudden marked increase of blood flow, which frequently follows the acute intake of an intoxicating dose of alcohol. This is the most plausible mechanism, since more prolonged heavy drinking did not increase the risk for this type of stroke. In other words, the circulatory effects of alcohol may not only dispatch emboli from the heart, but also artery-to-artery emboli from proximal arterial sources.

Recent heavy drinking either within the preceding week or 24 hours before the onset of stroke was also a risk factor for stroke of unknown origin. This was not an unexpected finding, because the embolic sources of ischemic stroke may easily remain undetected despite thorough investigation. We assume that our group of cryptogenic strokes included many subjects who actually had embolic stroke with a source that remained undiscovered. We did not observe any significant association between migrainous stroke and recent heavy drinking of alcohol. There was a negative rather than a positive association between recent drinking of alcohol and migrainous stroke (data not shown).

Our group of patients with verified cervicocerebral arterial dissection as the source of brain infarction showed a positive correlation with recent heavy drinking of alcohol. However, the series was too small to prove a statistically significant association. Traumatic cervicocerebral arterial dissection may well be a condition in which alcoholic intoxication is a significant and independent risk factor. Dissection does not always precipitate stroke, and if it does result in stroke, it may sometimes occur long after the arterial trauma. In fact, the trauma may have occurred several days before the onset of stroke. To prove an association between recent heavy drinking of alcohol and ischemic stroke due to dissection, one should know the intake of alcohol not only at the onset of the stroke but also at the moment that the index trauma is sustained.

In conclusion, the present study suggests that recent heavy drinking, including episodic and binge drinking, may trigger cardiogenic brain embolism. This is a new item on the list of hazards caused by heavy drinking of alcohol. Light drinking does not trigger cardiogenic brain embolism, and former heavy drinking is not a risk factor for cardioembolic stroke.

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References

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