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Alcohol Consumption and Atherosclerotic Burden in the Proximal Thoracic Aorta

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Abstract

BACKGROUND—The relationship between alcohol consumption and ischemic stroke or aortic atherosclerosis is unclear, but a protective effect of moderate consumption on stroke risk has been suggested. We conducted a cross-sectional analysis in a population-based sample to evaluate the possible association between alcohol consumption and aortic atherosclerotic plaque (AAP), which is associated with increased stroke risk.

METHODS—As part of the NINDS-funded Aortic Plaques and Risk of Ischemic Stroke (APRIS) study, 464 subjects over the age of 55 were studied (mean age 69.1±9.0 with 251 males and 213 females), including 255 patients with first ischemic stroke and 209 stroke-free controls. Transesophageal echocardiogram was performed for the detection of AAP. Alcohol consumption was measured in number of drinks per week during the previous year using a standardized questionnaire, and categorized as: (1) none or minimal (<1 drink per month); (2) light to moderate (between 1 drink per month and 2 drinks daily); and (3) heavy (>2 daily). Multivariate conditional logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence interval (CI) for alcohol consumption and AAP after adjustment for the potential confounding risk factors (age, sex, hypertension, diabetes, dyslipidemia, and cigarette smoking).

RESULTS—Overall, AAP were detected in 326 subjects (70.4%), and 174 subjects (37.6%) had AAP ≥ 4mm, which carry higher stroke risk. No or minimal alcohol consumption was present in 241 subjects (53.2%), and 177 subjects (39.0%) had light to moderate consumption. Prevalence of light to moderate alcohol consumption was significantly lower in stroke patients than in controls (35.5% vs. 60.3%, p<0.001) and in subjects who had AAP compared with those without it (41.6% vs. 58.8%, p=0.008). After adjusting for significant predictors of atherosclerosis, alcohol consumption of any degree was inversely associated with AAP (OR 0.61; 95%CI 0.37–0.98, p=0.042). The significance of the association was borderline for AAP ≥ 4mm (OR 0.64, 95%CI 0.41–1.00, p=0.054). In the dose-response analysis, only light to moderate alcohol consumption was significantly associated with a lower risk of having any AAP (adjusted OR 0.45; 95%CI 0.29–0.68, p<0.001) or AAP ≥ 4mm (adjusted OR 0.51; 95%CI 0.34–0.77, p=0.001).

CONCLUSIONS—Our data indicate that light to moderate alcohol consumption is associated with lower atherosclerotic burden in the proximal aortic arch. This observation may explain at least in part the lower risk of ischemic stroke observed in moderate alcohol consumers.

Keywords

aorta; atherosclerosis; stroke; alcohol drinking; risk factors

Background

In contrast to tobacco and illegal drugs, observational studies have shown an association between light-to-moderate alcohol consumption and decreased risk of ischemic stroke (IS).^{1–3} The mechanism underlying this association may involve prevention of atherosclerosis, although the reason for it is not well understood.⁴ Thus, additional data are needed for clarification, especially on the dose-response relationship of the association between alcohol consumption and atherosclerosis.

The measurement of thoracic aortic atherosclerotic plaque (AAP) thickness by transesophageal echocardiogram (TEE) is a well-validated technique for evaluating the progression of atherosclerosis.^{5–6} AAP is an increasingly recognized stroke risk factor, particularly among the elderly, and a plaque thickness cutoff of 4 mm is widely acknowledged as clinically relevant for risk stratification^{7–8} and has been used in numerous studies.⁹

The relationship between alcohol consumption and AAP is unclear. As part of the NINDS-funded Aortic Plaques and Risk of Ischemic Stroke (APRIS) study, we conducted a cross-sectional analysis in a population-based sample to compare the strength of the associations between alcohol consumption and the presence and thickness of AAP in the proximal thoracic aorta.

Methods

The Aortic Plaque and Risk of IschemicStroke (APRIS) study, in which TEE was performed in patients with acute ischemic stroke and in matching control subjects, affords a rare opportunity to examine risk factors associated with aortic arch atherosclerosis. All participants come from the Northern Manhattan area of New York City.

The participants in the APRIS study were recruited from a larger population-based cohort study among residents of northern Manhattan, the Northern Manhattan Study (NOMAS). The methods of subject recruitment and enrollment in NOMAS have been previously described.¹⁰ Since aortic AAP is rarely observed at a younger age, participants in APRIS were limited to those ≥ 55 years of age. The present report is based on 255 patients with first ischemic stroke consecutively referred for TEE, and 209 stroke-free controls drawn from the NOMAS cohort and matched to cases. One control subject was selected and matched to each stroke case by age (within 5 years), sex, and race-ethnicity. Stroke-free subjects were identified as part of NOMAS and invited to participate in APRIS. The first subject that matched a stroke patient according to the above criteria was enrolled as control. The study was approved by the Institutional Review Board at Columbia-Presbyterian Medical Center. All participants gave consent directly or through a surrogate when appropriate.

Baseline evaluation was performed at enrollment as previously reported.¹⁰ Standard techniques were used to measure blood pressure, height, weight, and fasting glucose.

Alcohol consumption was measured in number of drinks per week during the previous year using a standardized questionnaire.

The assessment of alcohol consumption was performed through structured in-person interviews using questions adapted from the National Cancer Institute food frequency questionnaire developed by Block et al¹¹ and the food frequency questionnaire of Willett et al.¹² The questions were modified to provide a defined frequency response set, as in the Willett questionnaire.^{12–13} Inquiries were made about consumption of 3 different forms of alcohol (wine, beer, and liquor) both during the past year and on average during the participant's drinking lifetime. The defined responses regarding frequency allowed 9 possibilities ranging from never to 7 or more drinks per day for each beverage type. The responses for each beverage type were then summed to obtain a total overall quantity. A standard drink was considered to be 120 mL of wine, 360 mL of beer, and 45 mL of liquor. Then, consumption of alcohol was categorized as: (1) none or minimal (<1 drink per month); (2) light to moderate (1 drink per month to 2 drinks daily); and (3) heavy (>2 daily). Multivariate conditional logistic regression analysis was used to calculate the odds ratios (ORs) for alcohol consumption and AAP after adjustment for the potential confounding risk factors (age, sex, hypertension, diabetes, dyslipidemia, and cigarette smoking).

Cardiovascular risk factors were collected by direct interview using standardized questions adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System or by medical record review.¹⁴ Hypertensive status was defined as a systolic blood pressure recording ≥ 140 mm Hg or a diastolic blood pressure recording ≥ 90 mm Hg based on the mean of the 2 readings of the blood pressure measurements, a patient's self-report of a history of hypertension, or antihypertensive medication use. A history of diabetes mellitus was defined by a patient's self-report of such a history, insulin use, oral hypoglycemic use, or a fasting glucose ≥ 126 mg/dL in a single measurement. Hypercholesterolemia was defined as total serum cholesterol > 240 mg/dL, a patient's self-report of hypercholesterolemia or the presence of lipid-lowering treatment. Fasting lipid panels (including total cholesterol, LDL, HDL, and triglycerides) were measured with a Hitachi 705 automated spectrometer (Boehringer). Cigarette smoking was defined by a current history of cigar or cigarette smoking (smoking within a year). Body mass index was calculated as weight (kilograms) divided by height (meters)squared. The presence of a trial fibrillation was documented based on the results of a current or past ECG. Coronary artery disease included history of myocardial infarction or typical angina or the patient's reporting of a positive diagnostic test (stress test, coronary angiography) or drug treatment. Carotid duplex Doppler examination to assess for stenosis was performed in 216 stroke patients (84.7%) and in 168 control subjects (80%).

The method for assessment of AAP has been described fully in previous publications.¹⁵ Briefly, TEE was performed with an Agilent 2500, 4500, or 5500 system with a 5MHz omniplane transducer. AAP in proximal thoracic aorta (i.e., proximal to the takeoff of the left subclavian artery) was assessed by a single experienced echocardiographer (MDT) blinded to the subject's risk factors. AAP thickness was measured in the horizontal plane, perpendicular to the major axis of the aortic lumen as previously reported.¹⁵ AAP was deemed present when its thickness was equal to or more than 2 mm. Large AAP was defined thickness equal to or greater than 4 mm. This cutoff has been shown to correlate with risk of stroke in prior studies⁷ and is generally accepted as clinically relevant^{14–18}. Echocardiographers performing the TEE were blinded to subject's lipid parameters and other risk factors.

Statistical Analysis

The distributions of alcohol consumption and other variables were examined. Differences between mean values were assessed by Student's t-test, between proportions by chi-square test. Univariate and multivariate logistic regression analyses were performed to test the association between alcohol consumption and AAP before and after adjustment for potentially confounding cardiovascular risk factors (age, sex, hypertension, diabetes, cholesterol and cigarette smoking). The same analyses were performed for stroke patients and control subjects separately. Statistical significance was determined at the $\alpha=0.05$ level with 2-sided tests. Statistical analyses were performed with SAS 9.1 computer software (SAS Institute).

Results

Baseline Characteristics

We enrolled 464 subjects (251 male, 213 female), including 255 patients with first ischemic stroke and 209 stroke-free controls. Participants were predominantly male (54.1%), elderly (mean age 69.1 ± 9.0) and hypertensive (76.3%; Table 1). The prevalence of hypercholesterolemia, diabetes, and cigarette smoking were 44.2%, 33.3%, and 58.4%, respectively. Atrial fibrillation was present in 8.9% of our cohort.

Carotid stenosis $>60\%$ was more frequent in stroke patients than in control subjects, as were many of the cardiovascular risk factors. Only one control subject (0.6%) had evidence of carotid stenosis $>60\%$ by Doppler ultrasound. The etiology of stroke was thought to be lacunar in 61 patients (23.9%), atherosclerotic in 51 patients (20.0%), cardioembolic in 43 (16.9%). A stroke of unknown cause (cryptogenic) was diagnosed in 92 of 255 stroke patients (36.1%).

Overall, AAP of any thickness was detected in 326 subjects (70.4%); 174 subjects (37.6%) had large AAP ($\geq 4\text{mm}$), 67 subjects (14.5%) had ulcerated or mobile AAP and 5 subjects (1.1%) had mobile and large AAP. Subjects with AAP were older (71.0 ± 9.0 vs. 64.6 ± 7.2 , $p<0.001$), more likely to smoke (62.6% vs. 48.9%, $p=0.006$) and to have hypercholesterolemia (47.7% vs. 36.6%, $p=0.028$) and coronary artery disease (15.5% vs. 5.8%, $p=0.004$). The number of subjects who had significant carotid stenosis ($>60\%$) increased as degree of AAP progressed. The prevalence was 3.6%, 7.5% and 10.9% for subjects with no AAP, any AAP and large AAP, respectively ($p=0.15$ for AAP vs. no AAP, and $p=0.006$ for large AAP vs. no AAP).

Alcohol Consumption—One hundred and thirty-six subjects (30.1%) consumed no or minimal alcohol, and 238 subjects (52.7%) and 78 subjects (17.2) had light to moderate and heavy consumption, respectively. Prevalence of alcohol consumption was significantly lower in stroke patients (35.5% vs. 60.3% in controls, $p<0.001$) and in subjects who had AAP (41.6% vs. 58.8% in subjects without AAP, $p=0.001$). After adjusting for other significant predictors of atherosclerosis, alcohol consumption of any degree was inversely associated with AAP (OR 0.61; 95%CI 0.37–0.98, $p=0.042$). Alcohol consumption at anytime during the lifetime also inversely trended for association with AAP, although it was not statistically significant (OR 0.65; 95%CI 0.36–1.16, $p=0.144$). Importantly, after adjustment for HDL, the strength of the association between alcohol and AAP remained similar (OR 0.66; 95%CI 0.40–1.08; $p=0.094$).

The significance of the association was borderline for AAP $\geq 4\text{mm}$ (OR 0.64, 95%CI 0.41–1.00, $p=0.054$). When stroke patients and control subjects were analyzed separately, the association patterns for alcohol consumption and AAP or large AAP ($\geq 4\text{mm}$) showed

similar trend as in the overall study group, but did not reach statistical significance (Table 2).

In the dose-response analysis, only light to moderate alcohol consumption remained significantly associated with a lower risk of having any AAP (adjusted OR 0.45; 95%CI 0.29–0.68, $p<0.001$) or AAP ≥ 4 mm (adjusted OR 0.51; 95%CI 0.34–0.77, $p=0.001$). When light to moderate consumption of alcohol was further divided into subcategories of low-moderate (LM: 1 drink per month to 1 drink per week) and high-moderate drinking (HM: 2–3 drinks per week to 2 drinks daily), LM was associated with a lower risk of having any AAP (OR 0.49; 95%CI 0.26–0.91, $p=0.025$) whereas HM was not (OR 0.67; 95%CI 0.40–1.14, $p=0.138$). The dose-response relationship is shown in Figure 1.

Discussion—Observational population studies consistently showed lower risk for atherothrombotic vascular disease, most notably coronary artery disease,^{16–17} among light drinkers than among non-drinkers. Our data indicate that light to moderate alcohol consumption is associated with lower atherosclerotic burden in the proximal thoracic aorta, which is strongly associated with IS, and underscore a possible mechanism for the suggested effect of light to moderate alcohol consumption towards decreasing the risk of IS. In recent data from US national health statistics, the association of alcohol consumption with decreased risk of cardiovascular disease mortality tended to be stronger than that for cerebrovascular mortality, and this finding has been observed in several cohorts.^{18–20} This might also be reflection of the strong contributions of hypertension and a trial fibrillation as risk factors for IS, both of which are positively associated at least with heavy drinking.

Alcohol influences a wide range of vascular and biomechanical functions that have potential cardioprotective effects. Mechanisms include regulation of lipids and fibrinolysis, decreased platelet aggregation and coagulation factors, beneficial effect on endothelial function, inflammation and insulin resistance.^{21–24} A large proportion of the decrease in cardiovascular risk associated with moderate alcohol consumption appears to be explained by factors related to glucose metabolism and inflammation/hemostasis.²⁵ The association between alcohol consumption and lower risk of cardiovascular disease has also been attributed in great part to an increase in HDL cholesterol.²¹ We have previously demonstrated that HDL cholesterol was inversely associated with progression of proximal aortic atherosclerosis, which also supports this hypothesis.²⁶ In the current study, the model that included both LDL and HDL cholesterol level showed only modest association between alcohol consumption and aortic atherosclerosis, which may suggest that part of the effect of alcohol may be mediated through its effects on HDL.

Previous studies have reported on the association between alcohol intake and subclinical atherosclerosis, the latter mainly being carotid atherosclerosis measured by carotid ultrasound. An analysis from the Bruneck and Kuopio study initially reported the highest carotid IMT among the heaviest drinkers.^{27–28} A community study from Germany demonstrated a J-shaped association between alcohol consumption and subclinical carotid atherosclerosis in men after controlling for major confounders.²⁹ Similarly, a quantitative analysis from the Cardiovascular Health Study revealed that consumption of 1 to 6 drinks per week was associated with less carotid atherosclerosis and consumption of 14 or more drinks was associated with greater atherosclerosis. Although our study population had relatively few heavy drinkers, our results are consistent with these studies and expand them to proximal aortic atherosclerotic plaque, which is a well known stroke risk factor.

An important strength of our study was its multiethnic community-based sample. The majority of subjects were Hispanics, followed by almost equal proportions of Caucasians and African-Americans. The current data on the effect of alcohol on stroke in multiethnic

adults are sparse. Previous studies were mostly based on non-Hispanic whites. These limited data suggest that the association seemed stronger in this ethnic subgroup and that the apparent U- or J-shaped associations of alcohol consumption with cardiovascular disease and mortality or morbidity may not apply to African-Americans or Hispanics.³⁰

In the 2006 AHA/ACC Guidelines for Secondary Prevention for patients with coronary and other atherosclerotic vascular disease, patients are encouraged to maintain a lifestyle that includes alcohol in moderation.³¹ Our finding of a slightly stronger correlation of alcohol with decreased AAP burden in patients with stroke compared to controls supports the current recommendation. However, the recent Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack³² also recommended that patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol and light to moderate levels of alcohol consumption may be reasonable, whereas nondrinkers should not be counseled to start drinking.

Limitations

The first limitation of our findings is that our study was observational, and our results might be confounded by other unmeasured factors. Residual confounding by education, physical, marital status (common correlates of alcohol drinking), may be a source of bias that might reduce the apparent benefit. Some of these social factors were available in our study as categorical variables (high school or higher education, marital status) and were, in fact, variably associated with alcohol consumption. After adjustment for these covariates, the negative association of alcohol consumption with AAP was of borderline significance (OR 0.61; 95% CI 0.37–1.00; $p=0.050$).

In the current study, there were 60.3% current drinkers and 84.2% lifetime drinkers. Under-reporting of alcohol consumption may result in a tendency for relative risks to be biased toward the null hypothesis. In fact, although higher than overall NOMAS cohort (37.7% and 71.9% for current and lifetime drinkers, respectively),³³ alcohol consumption observed in our study population was remarkably light, raising the possibility of under-reporting. In addition, the relatively high mean age of the population may have contributed to a lighter than expected consumption. In addition to the amount of alcohol consumed, other aspects of alcohol intake may be important. For example, choice of alcohol type and frequency of consumption may vary considerably over time, a circumstance for which we could not account.

Previous studies have suggested that the magnitude of the effects of alcohol differ between IS and hemorrhagic stroke, and the latter was not included in our study. Hemorrhagic stroke tends to be positively associated with alcohol consumption, perhaps related to the antiplatelet activity of alcohol.^{34–35} In addition, alcohol and medications can interact in a variety of situations that differ depending on the timing of alcohol and medication consumption and on the drinking pattern. However, the majority of these interactions occur among individuals who drink heavily, who were few in our study cohort.³⁶

Conclusion

This cross-sectional study suggests that light to moderate drinking is associated with lower risk of proximal aortic atherosclerosis. This observation may help explain in part the protective effect of moderate alcohol consumption on the risk ischemic stroke. Further study is warranted to clarify the magnitude of the effects of alcohol on the incidence of atherosclerotic events.

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Figure 1.
Dose-response relationship between alcohol consumption and aortic atherosclerosis.
(AAP=aortic atherosclerotic plaque)

Baseline Characteristics

Table 1

Baseline Characteristics	All Subjects n=464	Stroke Patients n=255	Control subjects n=209	P-value
Male gender (%)	54.1	52.2	56.5	0.35
Age (yr)	69.1	70.9	67	<0.001*
Atrial fibrillation (%)	8.9	11.6	5.8	0.031
Diabetes (%)	33.3	42.4	22.5	<0.001
Hypertension (%)	76.3	85.7	65.1	<0.001
Coronary artery disease (%)	12.6	17.1	7.2	0.001
Hypercholesterolemia (%)	44.2	40.3	48.8	0.069
Cigarette smoking (%)	58.4	56.8	60.3	0.45
Alcohol drinking in the past 12 months (%)	46.9	35.5	60.3	<0.001
Alcohol drinking during lifetime (%)	70.3	58.6	84.2	<0.001
Large AAP (≥ 4mm) (%)	37.6	48.8	23.9	<0.001
Any AAP (>1mm) (%)	70.4	77.2	62.2	<0.001

AAP=aortic atherosclerotic plaque

* The difference in age is due to the age matching strategy (±5 years), which casually resulted in an overall difference in mean values.

Table 2

Result of Univariate Analysis

	All Subjects			Stroke Patients			Controls		
	Any AAP (≥1mm)	Large AAP (≥4mm)	OR	Any AAP (≥1mm)	Large AAP (≥4mm)	OR	Any AAP (≥1mm)	Large AAP (≥4mm)	OR
Age	1.10	<.0001	1.06	1.09	<.0001	1.05	1.10	<.0001	1.04
Male gender	0.79	0.242	0.92	0.72	0.278	0.78	0.89	0.688	1.35
Diabetes	1.14	0.550	1.35	1.17	0.608	1.48	0.77	0.446	0.48
Hypertension	1.51	0.075	1.59	0.62	0.319	1.06	1.76	0.056	1.34
Cigarette smoking	1.75	0.007	1.66	1.90	0.034	1.94	1.75	0.054	1.55
Alcohol drinking in the past 12 months (%)	0.50	0.0009	0.53	0.68	0.210	0.68	0.48	0.016	0.64
Alcohol drinking during lifetime (%)	0.60	0.030	0.76	0.75	0.348	1.02	0.67	0.335	1.20
									0.691

AAP=aortic atherosclerotic plaque, OR=odds ratio