Alcohol Intake is Significantly Associated with Atrial Flutter in Patients under 60 Years of Age and a Shorter Right Atrial Effective Refractory Period

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Background: *Although evidence suggests that alcohol is associated with atrial fibrillation (AF), the association between alcohol and atrial flutter (AFL) has not been examined. The mechanism connecting alcohol and atrial arrhythmias is unknown.*

Methods: *Alcohol intake was determined in 195 consecutive patients with AF and AFL. Control subjects included patients with other supraventricular arrhythmias (n = 132) and healthy subjects (n = 54). Because of important competing risk factors for atrial arrhythmias in the elderly, stratification by age was performed. In a subset, atrial effective refractory periods (AERPs) were obtained from the high right atrium and proximal and distal coronary sinus.*

Results: *AF and AFL patients were significantly more likely to be daily alcohol drinkers (27% vs 14% of controls, P = 0.001). In multivariable analysis, AFL patients ≤ 60 years of age were significantly more likely to be daily drinkers than to drink no alcohol compared to controls (odds ratio 17, 95% confidence interval 1.6–192.0, P = 0.019). Progressively more frequent alcohol intake was significantly associated with a progressively greater odds of AFL in patients ≤ 60 years of age (P = 0.045). Neither AF subjects of any age nor AFL subjects > 60 years of age exhibited significant associations with alcohol after multivariable adjustment. Right AERPs shortened significantly with increasing amounts of alcohol intake (P = 0.025), whereas left AERPs were not associated with alcohol intake.*

Conclusions: *Alcohol intake is positively associated with AFL in younger patients. The mechanism may be related to a shortening of the right AERP. (PACE 2008; 31:266–272)*

atrial fibrillation, atrial flutter, alcohol, refractory period, atrial effective refratory period (AERP)

Introduction

Atrial flutter (AFL) has an incidence of 88 per 100,000 person-years, with approximately 200,000 new cases in the United States every year.[1] Although certain risk factors, such as age and male gender, have been identified,[1] the cause remains unknown in many patients. Atrial fibrillation (AF) and AFL, while mechanistically distinct, are often found in the same types of patients and are felt to be interrelated.[2] Although an association between AF and alcohol has been described,[3,4] the association between alcohol and AFL has not been investigated.

The mechanism by which alcohol increases the propensity toward atrial arrhythmias is unknown, and, given the apparent acute effects of alcohol on the emergence of the arrhythmia,[5] it makes sense that these effects would involve the more immediately mutable electrophysiology (EP) characteristics (rather than the physical/substrate properties) of the atria. Atrial refractoriness may be important to atrial arrhythmias,[6–9] and, to our knowledge, the association between alcohol intake and atrial effective refractory periods (AERPs) has not previously been examined.

We performed a case-control study to assess the association between alcohol intake and AF and AFL. Because the association between AF and alcohol use may be less evident in older subjects,[10,11] we stratified AF and AFL patients by age. The association between right and left (coronary sinus) AERPs and alcohol intake was also assessed.

No potential conflicts of interests exist.

Funding Sources: This work was made possible by grant number K12 RR024130 (G.M.M.) from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research, and the American Heart Association Western States Affiliate Beginning Grant-in-Aid Award (G. M. M.).

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Received September 18, 2007; revised October 15, 2007; accepted November 13, 2007.

Methods

Study Design and Subjects

We performed a prospective observational study of consecutive adult patients presenting for ablation or cardioversion of AF and AFL to a university medical center over a 2-year period. Over the same time period, consecutive patients presenting to the same electrophysiology laboratory for ablations of paroxysmal supraventricular tachycardia (SVT), including atrioventricular (AV) nodal reentrant tachycardia, AV reciprocating tachycardia, and focal atrial tachycardia, were enrolled as controls. A second control group of normal subjects with no known arrhythmias was also enrolled.

Data Collection

In addition to obtaining a medical history from chart review and patient interviews, each patient underwent a structured interview that included a standard question regarding average alcohol intake. A single drink of alcohol was considered to be equivalent to a glass of wine, a can of beer, or a shot of hard liquor/distilled spirits. Answers regarding alcohol intake were categorized as: (1) never (or none for >three months); (2) some alcohol in the last three months, but <1–2 drinks per month; (3) >1–2 drinks per month, but <1–2 drinks per week; (4) >1–2 drinks per week, but <1–2 drinks per day; (5) 1–2 drinks per day; and (6) >2 drinks per day. Daily alcohol use was defined as an average alcohol intake of one or more drinks of alcohol per day (the categories above were collapsed to 5 and 6 versus the rest). The association between the atrial arrhythmias was assessed in relation to daily alcohol consumption versus less than daily alcohol consumption (categories 1–4), as well as daily consumption versus no or rare consumption (category 1).

Patients undergoing invasive EP study, who presented with normal sinus rhythm, also underwent assessment of AERPs. In order to minimize the effects of a recent tachyarrhythmia, no one presenting in an arrhythmia at the start of their invasive procedure had AERPs obtained as part of the study protocol (including AERPs obtained after cardioversion or ablation to sinus rhythm). After placement of standard multipolar electrode catheters under fluoroscopic guidance in standard positions (including a coronary sinus catheter placed via the right internal jugular vein) and before any ablation or induction of tachycardia, AERPs were obtained at 400 ms drive cycle length at twice pacing thresholds from the high right atrium, proximal coronary sinus, and distal coronary sinus.

All patients provided witnessed and informed consent. The study was approved by the University of California, San Francisco (UCSF) Committee on Human Research.

Statistical Analysis

Normally distributed continuous variables are expressed as means ± standard deviation (SD).

Bivariate analyses of normally distributed continuous variables were assessed using Student's *t*-tests and categorical variables were compared using the χ^2 test. Multivariable analysis was performed with logistic regression analysis, and covariates/potential confounders were selected based on both important demographics (e.g., age, race, and gender) and those covariates significantly associated with both the predictors and outcomes of interest with P values <0.10 or covariates that substantially changed the regression coefficient (>20%).

In addition to assessing regular alcohol intake as a dichotomous predictor, progressive levels of alcohol were examined in the logistic regression model. In order to assess linear associations between progressive degrees of alcohol consumption with the outcomes after adjustment in the logistic regression model, Wald tests for trend were performed. Two-tailed P values of <0.05 were considered statistically significant.

Results

Three hundred eighty-one subjects were enrolled, including 195 cases (121 with AF and 74 with AFL) and 186 controls (132 with SVT and 54 with no known arrhythmia). Thirty-one (42%) of the AFL patients had a history of AF. Of all the subjects, 79 (21%) drank at least one drink of alcohol daily. The baseline characteristics of those with and without AF/AFL are shown in Table I. The baseline characteristics of those who drank alcohol daily are shown in Table II.

Daily Alcohol

Bivariate analysis revealed a significant association between AF/AFL and alcohol, with a similar proportion of daily drinkers in AF and AFL patients (Fig. 1). This significant bivariate association persisted after comparing AF and AFL versus controls with no arrhythmia alone (P = 0.031) or versus SVT patients alone (P = 0.006). In addition, comparisons between AF versus controls alone (P = 0.006) and AFL versus controls alone (P = 0.006) also demonstrated statistical significance. Within the AFL group, there were no differences in alcohol consumption between those with and without a history of AF. After adjustment for multiple potential confounders, the statistically significant association between AF/AFL and alcohol was lost. This attenuation was driven primarily by age

Table I.

Baseline Characteristics of Subjects with Atrial Fibrillation (AF) and Atrial Flutter (AFL) Compared to Controls. P Values Reflect Comparisons to the Control Group

	Control (n = 186)	AF or AFL (n = 195)	P Value	AFL (n = 74)	P Value
Race					
White	117 (65%)	147 (78%)		53 (73%)	
Black	7 (4%)	5 (3%)		3 (4%)	
Asian	26 (14%)	22 (12%)		11 (15%)	
Latino	17 (9%)	9 (5%)	0.045*	3 (4%)	0.65
Age (years)	45 ± 13	59 ± 12	<0.0001	61 ± 14	<0.0001
Male	84 (43%)	146 (75%)	<0.001	55 (74%)	<0.001
BMI (kg/m^2)	27 ± 10	29 ± 6	0.06	29 ± 6	0.18
Hypertension	33 (17%)	71 (36%)	<0.001	29 (39%)	<0.001
Type II diabetes	12 (7%)	22 (11%)	0.098	13 (18%)	0.006
Coronary artery disease	7 (4%)	22 (12%)	0.003	13 (18%)	<0.001
Ejection fraction (%)†	62 ± 6	58 ± 10	0.0051	58 ± 9	0.0170
Congestive heart failure	0	17 (8%)	<0.001	8 (11%)	<0.001
Cigarette smoking	25 (13%)	20 (9%)	0.25	6 (8%)	0.27

BMI = body mass index.
*This P value was driven primarily by the difference in whites (P = 0.008).
†Echocardiogram performed on 108 cases and 56 SVT patients.

and a weaker association between alcohol and AF than between alcohol and AFL.

After multivariable adjustment, there was no association between either AF or AFL when comparing those who drank daily and those who drank less than daily. However, after adjustment, patients ≤ 60 years of age (n = 255) who drank daily had a significantly greater odds of having AFL than those

Table II.

Baseline Characteristics of Subjects with Daily Alcohol Intake Compared to Those with Less than Daily Alcohol Intake

	Daily Alcohol (n = 79)	Less than Daily Alcohol (n = 302)	P Value
Race			
White	68 (85%)	212 (67%)	
Black	2 (3%)	10 (3%)	
Asian	2 (3%)	51 (16%)	
Latino	1 (1%)	28 (9%)	0.003*
Age (years)	59 ± 14	51 ± 16	<0.0001
Male	64 (77%)	183 (57%)	0.001
BMI (kg/m^2)	27 ± 5	28 ± 9	0.27
Hypertension	24 (29%)	89 (28%)	0.79
Type II diabetes	5 (6%)	34 (11%)	0.22
Coronary artery disease	6 (7%)	29 (9%)	0.62
Ejection fraction (%)†	59 ± 10	60 ± 9	0.51
Congestive heart failure	5 (6%)	14 (4%)	0.43
Cigarette smoking	8 (10%)	39 (12%)	0.54

BMI = body mass index.
*Significant pairwise comparisons versus all other races: whites (P = 0.004); Asians (P = 0.001); latinos (P = 0.019).
†Echocardiogram performed on 112 cases with daily alcohol intake and 46 with less than daily alcohol intake.

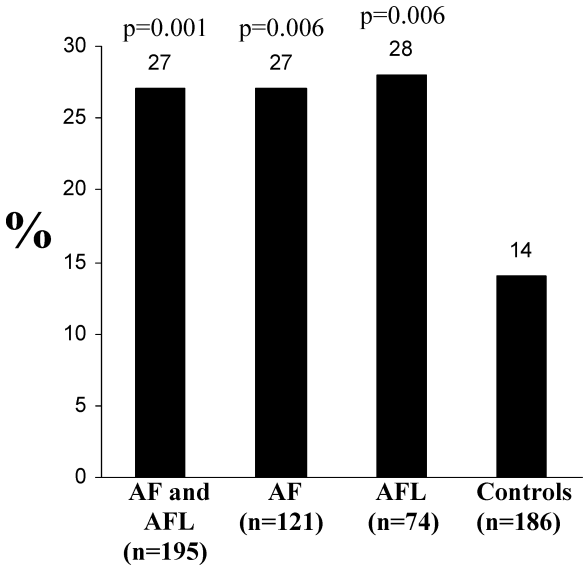

Figure 1. *Proportion of atrial fibrillation (AF) and atrial flutter (AFL) subjects and controls with daily alcohol intake. P values reflect comparisons to controls.*

who did not drink alcohol (odds ratio [OR] 17, 95% confidence interval [CI] 1.6–192.0, P = 0.019). As shown in Figure 2, a similar association was not observed for the AFL patients older than the age of 60 years nor in those with AF regardless of the age group. Adding those with AFL and a history of AF to the AF group did not result in any significant findings.

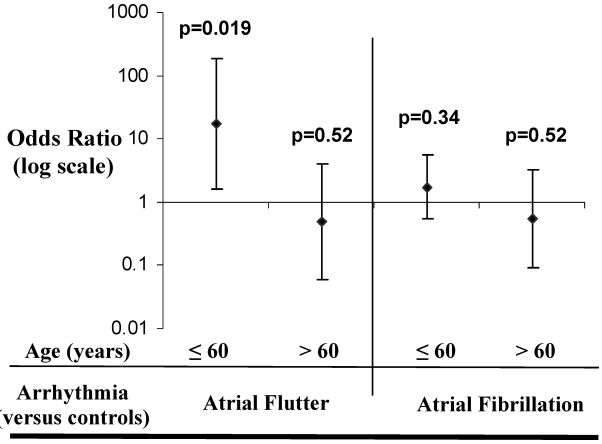

Figure 2. *Odds ratios (on the log scale) for the presence of arrhythmia in those who drink at least one alcoholic drink daily compared to those who do not drink alcohol after adjusting for age, gender, race, hypertension, congestive heart failure, coronary artery disease, and body mass index. Y error bars denote 95% confidence intervals.*

A test for interaction by differing effects of age (≤ or >60 years of age) on the relationship between regular alcohol intake and AFL favored a stronger effect of alcohol on AFL in the younger patients (OR 2.9, 95% CI 0.4–20.9), but was not statistically significant (P = 0.29).

Progressive Amounts of Alcohol

After multivariable adjustment, increasing amounts of alcohol exhibited an association with a greater odds of AFL that nearly reached statistical significance (P = 0.052, Table III). After stratifying by age and adjusting for multiple potential confounders, those subjects less than 60 years of age demonstrated a statistically significant linear association between increasing amounts of alcohol and a greater odds of having AFL (P = 0.045, Table IV). No linear association between progressively increasing amounts of alcohol and AF was observed.

Atrial Effective Refractory Periods

AERPs performed at 400 ms drive cycle length were available from the high right atrium in 48 patients (8 AF, 11 AFL, and 30 SVT), from the proximal coronary sinus in 43 patients (7 AF, 11 AFL, and 25 SVT), and from the distal coronary sinus in 40 patients (9 AF, 9 AFL, and 22 SVT). Thirty-six patients had AERPs available from all three sites. AERPs were not available when patients presented with tachycardia, when capture was inconsistent (particularly for coronary sinus pacing), or when the necessary pacing maneuvers initiated tachycardia. After adjusting for multiple potential

Table III.

Odds Ratios for the Presence of AFL (of All Ages) for Each Progressive Frequency of Alcohol Intake Compared to No Alcohol Intake after Controlling for Age, Gender, Race, Hypertension, Congestive Heart Failure, Coronary Artery Disease, and Body Mass Index (Linear Test for Trend, P = 0.052)

Alcohol Frequency (drinks)	Odds Ratio	95% Confidence Interval	P Value for Each Level Compared to No Alcohol
<1–2/month	0.97	0.30–3.10	0.960
>1–2/month <1–2/week	2.50	0.60–10.30	0.210
>1–2/week <1–2/day	1.60	0.50–5.30	0.420
1–2/day	2.30	0.71–7.50	0.170
>2/day	5.40	0.77–7.50	0.091

Table IV.

Odds Ratios for the Presence of AFL in Those ≤60 Years of Age for Each Progressive Frequency of Alcohol Intake Compared to No Alcohol Intake after Controlling for Age, Gender, Race, Hypertension, Congestive Heart Failure, Coronary Artery Disease, and Body Mass Index (Linear Test for Trend, P = 0.045)

Alcohol Frequency (Drinks)	Odds Ratio	95% Confidence Interval	P Value for Each Level Compared to No Alcohol
<1–2/month	4.1	0.66–24.9	0.130
>1–2/month <1–2/week	15.7	1.8–134.8	0.012
>1–2/week <1–2/day	5.0	0.77–32.6	0.089
1–2/day	11.4	1.4–89.6	0.021
>2/day	52.4	0.89–3073.8	0.057

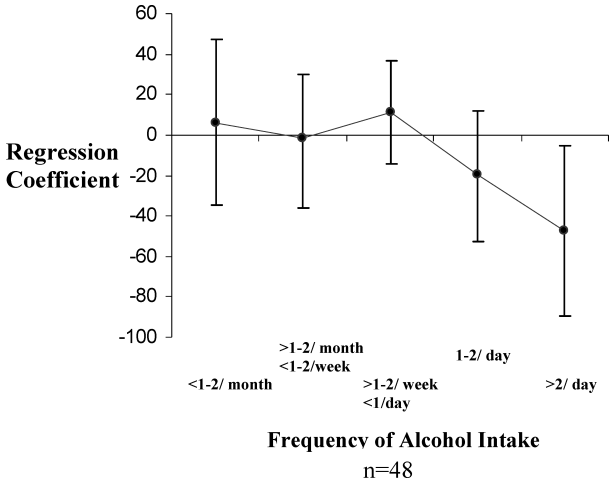

Figure 3. *Increasing intake of alcohol is associated with shorter high right atrial effective refractory periods (test for linear trend, P = 0.025). The Y-axis represents linear regression coefficients for atrial effective periods (ms) obtained from the high right atrium after adjusting for age, gender, and race. Y error bars denote 95% confidence intervals.*

confounders, greater alcohol intake was associated with a lower high right AERP (Fig. 3). In addition to a statistically significant linear trend (with lower AERPs obtained from the high right atrium associated with greater degrees of drinking, P = 0.025), those who drank more than two alcoholic drinks per day had, on average, a high right AERP that was about 50 ms shorter than those who drank no alcohol (P = 0.028). Although the smaller numbers within each arrhythmia subgroup (i.e., AF, AFL, and SVT) alone were insufficient to detect a statistically significant finding related to high right AERP and alcohol, each group exhibited a similar trend, with the lowest high right AERPs found in the heaviest drinkers. Neither the proximal nor distal coronary sinus ERPs exhibited a similarly significant linear association with greater degrees of alcohol intake (P = 0.87 for the proximal coronary sinus and P = 0.70 for the distal coronary sinus). In addition, those who drank more than two alcoholic drinks a day did not exhibit statistically significantly shorter ERPs in the proximal or distal coronary sinus.

Discussion

Compared to those with no alcohol consumption, daily alcohol intake was significantly associated with the presence of AFL in subjects ≤60 years of age. In the same age group, progressive amounts of average alcohol intake also demonstrated a progressive association with AFL. In addition, increasing alcohol intake was associated with shorter right AERPs, suggesting a mechanism by which alcohol may make patients more prone to AFL.

Previous studies examining the connection between alcohol and atrial arrhythmias have focused on AF: early studies demonstrated an association with acute alcohol consumption,[5,12] and both older and more recent data suggest there is an association between AF and heavy alcohol use.[4,13,14] Data from large cohort studies have been conflicting,[3,4,10,11] but the negative findings arise from studies only involving subjects ≥ 65 years of age.[10,11] Although not statistically significant in our study, a test for interaction provided a point estimate in favor of a greater effect of alcohol with regard to AF in the younger age group. As this test is often insufficiently powered, a P value of >0.05 (as in this case) does not disprove the presence of a true interaction. Due to prevalent competing risk factors for AF and AFL in the older population (particularly as the most important risk factors are age itself and hypertension, also associated with aging),[15,16] we believe the association between alcohol and AF/AFL may become diluted in older age groups, making it more difficult to elucidate. Finally, age was also an important confounder in this relationship, particularly in the older age group, and we may have had insufficient power to detect a relationship between alcohol and AF in the older age group after adjustment for age.

We did not find any association between alcohol and AF, and there are several potential

explanations for this: first, unlike previous positive studies, we did not examine acute intoxication as a risk factor for recent-onset AF. Second, whereas previous studies found associations between alcohol and AF only in people who drank heavily (such as 35 drinks per week[4] or more than three drinks a day[13]), we did not quantitate exact amounts of alcohol in those who drank more than two glasses a day, and, therefore, may have missed a true association present in that subgroup. One large cohort study found a statistically significant trend between increasing amounts of alcohol intake and risk for AF,[3] and our study may have been too small to detect such a relationship.

The association between alcohol and AFL has not specifically been previously described, and, given our negative findings regarding AF, our study suggests that the association may, in fact, be more important than that between alcohol and AF. Of note, one study may have included patients with AFL only because arrhythmia patients were identified by an International Classification of Diseases (ICD)-9 code common to both AF and AFL (without knowledge in that study as to if any, or how many, had AFL),[3] but exact risks in the AFL group and comparisons between AF and AFL could not be performed.

Importantly, no previous study has demonstrated a mechanism by which alcohol might make patients more prone to atrial arrhythmias. One canine study failed to reveal a clear mechanism, but also found that the duration of induced AF was longer in the control dogs rather than in those who received ethanol (i.e., an effect opposite to what was expected).[17] It is known that AF and AFL are interconnected and perhaps interdependent,[2] and it is, therefore, possible that, at least in some patients, alcohol may lead to AF via increasing the risk of AFL. To our knowledge, no previous studies have examined AERPs in relation to alcohol intake. AF has been associated with a short right AERP,[18] and right AERPs have been found to be shorter than left AERPs in subjects with AF and AFL.[19] While the importance of atrial refractoriness in atrial arrhythmias is now well established,[6–9] the mechanism by which a shorter right AERP might make patients more prone to AFL is not immediately evident. One possibility is that the shorter right AERP allows the right atrium to sustain a rapid rate in response to an initiating rhythm (such as atrial tachycardia and/or AF), or to more likely allow propagation of a critically timed premature atrial complex—in either case, the supposition is that, while conduction is enabled in the majority of the right atrium, the crista terminalis experiences conduction block in these scenarios, constructing the substrate for the macroreentrant circuit.[20] We can also not exclude the possibility that alcohol is simply an epiphenomenon or surrogate related to some other factor that might increase a patient's propensity to have AF and a shorter right AERP. For example, those who drink more alcohol may have elevated right atrial pressures, or may more often smoke tobacco, with the true causal association found in these related factors.

It is also not clear why alcohol might have different EP effects on the right and left atria, but speculation based purely on anatomy suggests that metabolism of either alcohol itself or an important metabolite of alcohol in the lung might play a role: at least some alcohol content is lost with respiration,[21] and some metabolism of alcohol occurs in the lung.[22,23] However, whether there are clinically meaningful differences in ethanol concentrations (or concentrations of a potentially important metabolite) in the right and left atria is, to our knowledge, unknown. Future experiments aimed at answering this question might simply involve measuring simultaneous alcohol levels (and levels of known important metabolites) in the venous and arterial circulations.

Finally, our data are insufficient to determine if the effects of alcohol on the atria are related to chronic effects (such as remodeling of ion channels or a change in the physical substrate) or acute effects due to the most recent intake (with more lingering alcohol and/or metabolites on the day of the procedure in those that drink more heavily). This association requires further study for validation purposes, and potentially a deeper mechanistic understanding.

Study Limitations

Our study has several limitations. First, because ejection fractions were not available in all patients, we were unable to include exact measurements of systolic function in our multivariable analysis. However, we did have clinical data regarding any history of congestive heart failure and coronary disease, and included these covariates in the model. We cannot exclude the possibility that some patients with AF discontinued or reduced their alcohol intake due to their diagnosis of AF, and therefore underreported their actual long-term use. However, whereas such a bias may contribute to our negative findings regarding AF, it would not have created a false-positive association with AFL. As our primary positive finding was found after analyzing several subgroups (more than one group of subjects by age, and AF and/or AFL as outcomes), we cannot exclude the possibility that chance alone is responsible for our findings; however, both our point estimate (OR of 17) and P value (0.019) for our findings related to

alcohol and AFL in younger patients are quite robust. Finally, AERPs could not be obtained in all patients, leading to analyses depending on smaller numbers; however, because AERPs were obtained in only patients presenting with sinus rhythm, it is unlikely that differences in AERPs were caused by differences in rhythm. In fact, because the majority of AERPs were obtained in control patients, the association between heavier alcohol use and right AERPs, independent of AF/AFL, is even more apparent.

Conclusion

Our study demonstrates a significant positive association between alcohol use and AFL in younger patients. The mechanism by which this occurs may involve an alcohol-induced shortening of right AERP.

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