PREVENTION

Commonly Consumed Beverages in Daily Life: Do They Cause Atrial Fibrillation?

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ABSTRACT

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in the United States and worldwide. Caffeine, alcohol, and, more recently, energy drinks are the most commonly consumed beverages in daily living, especially by young individuals. Several questions have been raised about the implications of caffeine, alcohol, and energy drinks in cardiovascular health, especially in triggering AF. This review focuses on the role of these commonly consumed beverages as a cause of AF, with special emphasis of potential mechanisms and studies addressing this issue.

Introduction

Atrial fibrillation (AF) currently affects >2 million individuals in the United States and is projected to affect about 5.6 million individuals by 2050.[1] Atrial fibrillation accounts for up to 20% of all ischemic strokes and increases the risk of stroke by 5-fold and the risk of mortality by 2-fold.[1,2] In addition to the traditional causes of AF, there has been a paradigm shift in the recognition of novel precipitating factors, including the metabolic syndrome, obesity, sleep apnea, exercise, and dietary intake of stimulants, which could have important prognostic and therapeutic implications.[3,4]

Caffeine, alcohol, and, more recently, energy drinks are the most commonly consumed beverages in daily living, especially by young individuals. Several questions have been raised about the implications of caffeine, alcohol, and energy drinks in cardiovascular health, especially in triggering AF. Recent studies have reported that there may be some association between amount of alcohol consumption and development of AF.[5–7] The role of caffeine in AF has been extensively debated over the past decade, and a causal effect could not be established.[8–13] Energy drinks are a new group of stimulant beverages that are rapidly growing in today's market and are used avidly among teenagers and young adults. These beverages are known to contain a substantial amount of caffeine along with other stimulants, such as taurine, sugar, vitamins, and herbs.[14] A few recent case reports have highlighted the development of arrhythmias, including AF, upon acute ingestion of energy drinks[15,16]; however, the effects of long-term consumption on AF are unknown. Similarly, the effects of caffeine, alcohol, and energy drinks on patients with preexisting AF and multiple other medical comorbidities remain unknown. This review focuses on the role of these commonly consumed beverages as a cause of AF, with special emphasis of potential mechanisms and studies addressing this issue (Table 1).

Caffeine

Possible Mechanism of Caffeine as a Cause of Atrial Fibrillation

Over the years, anecdotal reports have fostered the notion that caffeine can cause AF. As a known stimulant, this association was deemed biologically plausible. Caffeine is a methylxanthine compound that primarily causes neurohormonal stimulation and activation of the sympathetic nervous system by inhibiting phosphodiesterase and adenosine A_1, A_{2A}, A_3, and A_{2B} receptors and increases calcium concentration in the cytoplasm by blocking the reuptake of calcium in the sarcoplasmic reticulum.[17] Animal studies have demonstrated decrease in AF propensity after selective blockade of the adenosine A_1 receptor.[18,19] Acute caffeine consumption was reported to increase plasma renin and norepinephrine and epinephrine levels, increasing blood pressure and heart rate,[20] but had no effect on P-wave dispersion,[21,22] both suggested to be electrocardiographic (ECG) markers of AF

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Table 1. A Summary of the Studies Exploring the Association Between Caffeine and Alcohol in AF

Author	Type of Study	No. of Subjects	Follow-up, y	Results
Caffeine				
Frost et al[11]	Prospective observational	47 949	5.7	HRs (95% CIs) for increasing quartiles: 1.12 (0.87-1.44), 0.85 (0.65-1.12), 0.92 (0.71-1.20), 0.91 (0.70-1.19).
Conen et al[8]	Prospective observational	33 638	14.4	HRs (95% CIs) for increasing quartiles: 0.88 (0.72-1.06), 0.78 (0.64-0.95), 0.96 (0.79-1.16), 0.89 (0.73-1.09); $P = 0.45$.
Klatsky et al[12]	Prospective observational	130 054	17.6	HRs (95% CIs) for <1 cup of coffee/day, 1.0 (0.9-1.1, $P = 0.7$); 1–3 cups/day, 0.9 (0.8-1.0, $P = 0.2$); ≥4 cups/day, 0.8 (0.7-0.9, $P = 0.002$).
Shen et al[9]	Prospective observational	4526	4	HRs (95% CIs) for increasing quartiles: 0.84 (0.62-1.15), 0.87 (0.64-1.2), 0.98 (0.7-1.39); $P = 0.84$.
Mukamal et al[31]	Prospective observational	1369		HRs (95% CIs) 0.68 (0.45-1.02) for 1– < 3 cups/day; 0.56 (0.37-0.85) for 3– < 5 cups/day; 0.52 (0.34-0.83) for 5– < 7 cups/day; and 0.58 (0.34-0.98) for ≥7 cups/day, $P = 0.06$.
Caldiera et al[32]	Meta-analysis	115 993	N/A	Caffeine was not associated with an increased risk of AF (HR: 0.92, 95% CI: 0.82-1.04).
Cheng et al[33]	Meta-analysis	228 465	N/A	Caffeine was associated with a reduced risk of AF (RR: 0.90, 95% CI: 0.81-1.01, $P = 0.07$).
Alcohol				
Mukamal et al[46]	Prospective cohort	16 415	3	Alcohol consumption of ≥35 drinks/wk among men increased AF risk (HR: 1.45, 95% CI: 1.02-2.04).
Frost et al[47]	Prospective observational	47 949	5.7	Increased alcohol consumption increases AF risk in men and moderate alcohol did not increase risk of AF in women. Men in the highest quintile consumed 68.7 ± 22.8 g/day and had an increased AF risk (HR: 1.46, $P < 0.04$).
Djoussé et al[48]	Prospective		>50	Alcohol categories of 0.1–12, 12.1–24, 24.1–36, and >36 g/day had RRs (95% CIs) of 0.97 (0.78-1.22), 1.06 (0.80-1.38), 1.12 (0.80 -1.55), and 1.34 (1.01-1.78), respectively.
Conen et al[49]	Prospective observational	34 715	13	Alcohol consumption of 0, >0– < 1 drink/day, >1– < 2 drinks/day, and >2 drinks/day had HRs (95% CIs) for incident AF of 1, 1.05 (0.88-1.25), 0.84 (0.58-1.22), and 1.60 (1.13-2.25), respectively.
Samokhvalov et al[6]	Meta-analysis	67 891	N/A	Women with alcohol consumption of 24, 60, and 120 g of alcohol daily had RRs (95% CIs) of 1.07 (1.04-1.10), 1.42 (1.23-1.64), and 2.02 (1.60-2.97), respectively. Men, with similar consumption: 1.08 (1.04-1.11), 1.44 (1.23-1.69), and 2.09 (1.52-2.86), respectively.
Sano et al[50]	Meta-analysis	8602	6.4	HRs (95% CIs) for alcohol consumption of <23 g/day, 23–46 g/day, 46–69 g/day, and >69 g/day (heavy consumption) were 1.30 (0.68-2.49), 0.89 (0.60-1.32), 1.19 (0.73-1.95), 1.36 (0.79-2.35), and 2.90 (1.61-5.23), respectively.
Liang et al[51]	Prospective observational	30 433	4.6	Moderate consumption, HR: 1.14, 95% CI: 1.04-1.26; high consumption, HR: 1.32, 95% CI: 0.97-1.80.
Kodama et al[5]	Meta-analysis	130 820	N/A	RR for an increase in alcohol intake by 10 g/day was 1.08 (95% CI: 1.05-1.10, $P < 0.001$).

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; N/A, not applicable; RR, relative risk.

risk.[23] Electrophysiological testing with caffeine loading did not have an effect on interatrial and intra-atrial conduction intervals.[24] Experiments in dog models with intravenous caffeine also demonstrated lowering of the window of vulnerability (which is the interval difference between the longest coupling premature beat and the shortest), a measure of the propensity for AF inducibility.[19] A number of studies demonstrated that stimulated adenosine receptors play different roles in the pathogenesis of fibrosis, depending on the tissue.[25,26] The stimulation of adenosine A_{2B} receptors in the heart was shown to inhibit cardiac fibroblast production of collagen in vitro and diminish myocardial remodeling after a myocardial infarction.[27,28] Studies examining the effects of caffeine in cardiac fibrosis are limited. Finally,

coffee and tea are known to be important sources of antioxidants, such as phytochemicals and polyphenols, which may decrease inflammation and endothelial dysfunction.[29] These substances may be protective against AF as well.[30]

Assessing the Relationship of Caffeine and Atrial Fibrillation

Several studies have investigated the role of chronic caffeine consumption as a cause of AF and overall have reported no increased risk of AF (Table 1). The Danish Diet, Cancer, and Health prospective cohort study,[11] including 47 949 patients with a follow-up of 5.7 years, reported that there was no risk of AF with consumption of caffeine across all quintiles. The mean consumption of caffeine was 248 ± 91 mg/day and 994 ± 144 mg/dL in the highest quintile; both are substantially greater than the usual daily consumption of caffeine in the United States (22–33 mg/dL).

These findings were further supported by the Women's Health Study, a prospective cohort including 33 638 patients with a mean follow-up of 14 years, which showed no increased risk of AF in women free from cardiovascular disease across all quintiles of caffeine consumption.[8] Furthermore, subjects in the third quintile of caffeine consumption (285 mg/day) had a 22% lower risk of AF (95% confidence interval [CI]: 0.64-0.95). The study suggested that low to moderate caffeine consumption might be protective in AF. Another large population-based study including 130 054 participants reported an inverse relation of coffee drinking to risk of hospitalization for arrhythmias, especially AF (hazard ratio [HR]: 0.84, $P = 0.05$ in the 4–6 cups/day group and HR: 0.73, $P = 0.02$ in the group that consumed >6 cups/day).[12] The findings remained consistent with age, race, or sex. Similar results were reported by a longitudinal analysis of the Framingham Study in a 4-year follow up across all quintiles ranging from 23 mg/day to 452 mg/day of caffeine consumption.[9] The Stockholm Heart Epidemiology Program,[31] which consisted of 1369 patients hospitalized with a first episode of acute myocardial infarction, reported that when compared with <1 cup/day coffee consumers, there was a 30% lower risk of AF (which was not statistically significant) in the 4 higher categories of coffee consumers. A recent meta-analysis by Caldeira et al including 115 993 individuals reported that caffeine was not associated with an increased risk of AF (odds ratio [OR]: 0.92, 95% CI: 0.82-1.04, $P = 0.7$).[32] Low caffeine intake may produce a lower risk of AF (OR: 0.85, 95% CI: 0.78-0.92; I^2: 0%). This meta-analysis, though, provides valuable information about the consumption of caffeine in AF. It is important to note certain limitations, such as wide heterogeneity among patients included in the various trials; and several trials have used only coffee as a marker of caffeine intake, whereas a few have included other caffeinated beverages as well. It is also important to note that the estimation of caffeine content varies based on geographic differences in coffee preparation. Another recent meta-analysis including 228 465 patients reported that caffeine was associated with a reduced risk of AF (relative risk [RR]: 0.90, 95% CI: 0.81-1.01, $P = 0.07$).[33] In subgroup analyses, higher intake of caffeine was associated with a further reduced risk of AF (RR: 0.88, 95% CI: 0.78-0.99, $P = 0.13$) when compared with lower intake (RR: 0.94, 95% CI: 0.83-1.07, $P = 0.02$). Habitual caffeine intake reduced AF incidence by 14%.

Although the results from these large clinical trials strongly demonstrate that caffeine does not increase the risk of AF, there were limitations. The accuracy of self-reporting caffeine intake is subject to question. In addition, the investigators did not adjust for other confounding variables, such as smoking and sleep apnea. Although several trials have analyzed the effects of caffeine on the heart, further large-scale randomized clinical trials are necessary to better understand the specific effects of caffeine on AF.

Energy Drinks

Energy drinks are a relatively new phenomenon. They contain stimulants and other substances, including large amounts of caffeine, taurine, ginseng, guarana, theophylline, sugars, vitamins, and herbs, and are very popular among young adults and athletes.[14] The US Food and Drug Administration does not adequately regulate the marketing of energy drinks in the United States. The caffeine content in these energy drinks ranges from 50 mg to 500 mg.[34] Energy drinks such as Monster, Red Bull, and Full Throttle contain other ingredients such as carbohydrates, taurine, amino acids, guarana, ginseng, riboflavin, and thiamine in addition to high doses of caffeine.[35] Recently, isolated case reports have been published reporting cardiac arrhythmias, including AF, triggered by energy drinks.[14,15] The mechanism of this phenomena is unclear, as previous studies involving high doses of caffeine have shown no increased risk of AF.[8,9] The arrhythmia is reported to occur following acute ingestion of energy drinks in young adults. It is unknown whether these individuals had a genetic susceptibility that predisposed to the arrhythmia. It is also possible that the other ingredients and herbs in these energy drinks could potentially trigger an arrhythmia. One study reported that although no significant ECG changes were observed with energy drinks, subjects' systolic blood pressure increased by 10 mm Hg and heart rate increased by 5 to 7 beats per minute.[36] Little information exists concerning the ECG effects of energy drinks. Long-term data concerning the risk of chronic consumption of energy drinks in triggering AF are unknown, as studies have demonstrated increased blood pressure and heart rate upon acute consumption of energy drinks.[37,38] Further studies are necessary to determine whether energy drinks are associated with AF.

Alcohol

Possible Mechanism of Alcohol as a Cause of Atrial Fibrillation

Ethanol as a cause of AF is more commonly described in literature in the setting of acute consumption, a phenomenon commonly described as the "holiday heart."[39,40] The mechanism of alcohol-induced AF is complex and multifactorial and involves decreased vagal tone, an increased adrenergic state, increased levels of serum catecholamine, and electrolyte imbalance causing cardiac conduction and repolarization abnormalities such as prolongation of the P-R,

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QRS, and QTc intervals.[40] Experimental studies in animal models have produced conflicting information on the effects of alcohol in AF. One study reported that intravenous infusion of alcohol in rabbits reduced the inward sodium current (INa) and the outward calcium current (ICa-L) but had no effect on the outward potassium current, a phenomenon that may shorten the atrial refractory period and help promote AF.[41] Similar findings were reported by Klein et al in human embryonic kidney 293 cells. In that study, alcohol infusion reduced INa, which caused downregulation of sodium channels, which could lead to a decrease in the action potential duration, which might reduce the threshold risk for AF.[42] However, other studies have reported decrease in AF with alcohol infusion.[43,44]

Chronic heavy alcohol consumption can be associated with alcohol-induced cardiomyopathy, which can be associated with other traditional risk factors for promoting the progression of atrial fibrosis and, subsequently, AF.[5] A study by Greenspon et al on 14 patients with history of alcohol abuse reported that the prolonged heart rate variability interval, increased heart rate, and corrected sinus node recovery time all shortened with the acute ingestion of heavy alcohol on electrophysiological testing.[45] It may be speculated that there may be a J-shaped phenomenon seen with alcohol on cardiovascular effects AF. However, further research is necessary to further understand this mechanism.

Studies Assessing the Relationship of Alcohol and Atrial Fibrillation

Several studies have examined the acute and chronic effects of alcohol on AF. The large Copenhagen City Heart Study, a prospective cohort study including 16 415 subjects, showed that men who consumed >35 drinks per week had the highest risk of AF (HR: 1.45, 95% CI: 1.02-2.04).[46] In a prospective cohort Danish Diet, Cancer, and Health Study including 47 949 subjects, there was a modest increase in the risk of AF with increased alcohol consumption in men, whereas moderate consumption of alcohol did not seem to be associated with risk of AF in women.[11] Men in the highest quintile consumed 68.7 ± 22.8 g/day and had a HR of 1.46 ($P < 0.04$). These findings were similar to the Framingham Study,[48] which reported that long-term moderate alcohol consumption did not increase AF risk, whereas heavy alcohol consumption (>36 g/day) significantly increased risk of AF. However, the Women's Health Study,[49] a prospective randomized controlled trial including 34 715 healthy subjects, reported that consumption of 0 to 2 alcoholic beverages per day was not associated with an increased risk of AF, whereas consuming >2 or more alcoholic beverages per day increased risk of AF by 1.6× (95% CI: 1.13-2.25) in healthy middle-aged women when compared with nondrinkers. The differences noted in the above studies can be attributed to fewer women consuming higher quantities of alcohol in the previous studies and a higher percentage of patients with preexisting cardiovascular diseases.

Two main observations can be made from the existing meta-analysis, one reporting a threshold effect and the other a linear effect of alcohol on the risk of AF.[5,6] First, in the meta-analysis by Samokhvalov et al,[6] the risk of AF was only significant for intake of >3 alcoholic beverages per day (ethanol 36 g/day) for men and >2 alcoholic beverages per day (ethanol 24 g/day) for women. Furthermore, women who consumed <2 alcoholic beverages per day and men who consumed <3 alcoholic beverages per day did not demonstrate an increased risk of AF. This meta-analysis provided additional insight into the dose–response relationship between AF and alcohol consumption, implying a possible threshold above which there is a significantly increased risk of AF in both men and women. This concept of threshold effect of alcohol on AF was further reported in other recent studies.[5,50] In a study performed in Japan, the Circulatory Risk in Communities Study,[50] a higher incidence of AF was observed among participants with an ethanol intake >69 g/day, compared with never-drinkers. Another study[51] including 30 433 subjects who had no AF at baseline reported that higher levels of alcohol consumption had an increased risk of incident AF (HR: 1.14, 95% CI: 1.04-1.26 for moderate consumption [2 alcoholic beverages per day in women and 3 alcoholic beverages per day in men]; HR: 1.32, 95% CI: 0.97-1.80 for high consumption [>2 alcoholic beverages per day in women and >3 alcoholic beverages per day in men]). However, this threshold effect that the authors described would be different in each individual and would depend on several factors, such as age, race, ethnicity, sex, and other comorbidities. The recent meta-analysis by Kodama et al[5] reported that the association between alcohol intake and AF risk was more linear rather than J-shaped. The estimated RR for an increase in alcohol intake by 10 g/day was 1.08 (95% CI: 1.05-1.10, $P < 0.001$), suggesting that a moderate intake of alcohol could produce a significant risk of AF, compared with abstinence. Despite providing valuable information regarding the effect of alcohol on AF, the above-described meta-analysis suffers from several drawbacks, including heterogeneous reporting of alcohol consumption in study subjects, the presence of confounding variables, and failure to account for the development of alcohol-induced hypertension in heavy drinkers, which could increase the risk of AF.

A recent Swedish prospective study and a meta-analysis including 79 019 men and women with 859 420 patient-years of follow up reported that consuming a moderate amount of alcohol increased the risk of AF.[7] The study reported that the RR of AF was 1.01 (95% CI: 0.94-1.09) in those who consumed 1 to 6 alcoholic beverages per week; a RR of 1.07 (95% CI: 0.98-1.17) with 7 to 14 alcoholic beverages per week; a RR of 1.14 (95% CI: 1.01-1.28) with 15 to 21 alcoholic beverages per week; and a RR of 1.39 (95% CI: 1.22-1.58) in those who consumed >21 alcoholic beverages per week, compared with subjects who consumed <1 alcoholic beverage per week. In a meta-analysis consisting of 7 prospective trials and 12 554 AF cases, when compared with nondrinkers, the RR was 1.08 (95% CI: 1.06-1.10) with the consumption of 1 alcoholic beverage per day; 1.17 (95% CI: 1.13-1.21) with 2 alcoholic beverages per day; 1.26 (95% CI: 1.19-1.33) with 3 alcoholic beverages per day; 1.36 (95% CI: 1.27-1.46) with 4 alcoholic beverages per day; and 1.47 (95% CI: 1.34-1.61) with 5 alcoholic beverages per day. Furthermore, no significant differences in AF risk were observed by geographic region (North America and Europe) or by AF type. However, the

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most surprising finding of the study was the association of AF with the type of beverage. When stratified by the type of alcohol consumed, the relationship with AF was strongest with liquor, then wine, and weakest with beer. This study has several limitations, including observational design, self-reporting of alcohol consumption, and other covariates such as smoking, obesity, and a history of hypertension. The study only reported AF incidence identified in hospitalized or symptomatic patients, increasing the risk of leaving out a large population of patients with asymptomatic or silent AF.

Conclusion

There is no convincing evidence regarding the role of caffeine in causing AF in healthy individuals. Our review of literature has suggested that chronic ingestion of caffeine does not cause AF in healthy individuals. The effect of caffeine in patients with preexisting AF remains unknown due to lack of longitudinal studies. Almost all of these data are in relatively healthy subjects and cannot be extrapolated to all patients. Energy drinks are loaded with high doses of caffeine, sugar, and other chemicals that can potentially stimulate the heart. However, the acute and chronic effects of energy drinks in triggering AF are unknown. Further research is necessary in this area. Until then, it may be reasonable to either limit or avoid their use in patients with arrhythmias, including AF. Recent studies have shown that chronic moderate to heavy alcohol use seems to be associated with AF. Whether alcohol itself affects the progression of AF, including electrical and structural remodeling, remains unclear. However, it is recommended that patients with AF limit their alcohol use.

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