

Alcohol and arrhythmias

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Abstract

Introduction

Epidemiological, animal and human intervention studies suggest alcohol consumption has both beneficial and detrimental effects on cardiovascular health. While light to moderate alcohol consumption can produce cardioprotective effects, bingeing and abuse can lead to cardiomyopathy, heart failure, strokes, arrhythmias and sudden cardiac death. In this report, we review historical and recent studies investigating the association between alcohol and arrhythmias. We also discuss proposed mechanisms of alcohol-induced arrhythmogenesis.

Conclusion

There appear to be a plethora of mechanisms underlying alcohol-induced arrhythmias, including electrolyte abnormalities, rebound and adrenergic hypersensitivity, QT interval prolongation, decreased heart rate variability and atrial effective refractory period, and more. Clearly, the only advice that can be given to any patient suffering an alcohol-induced arrhythmia at this time is abstinence and a healthier lifestyle.

Introduction

Alcohol, a term used interchangeably with ethanol or ethyl alcohol, refers to the colourless, volatile and intoxicating constituent found in wine, beer and distilled spirits. Alcohol is one of the most commonly consumed recreational substances worldwide. The World Health Organization (WHO) estimates annual

alcohol consumption at 6.13 L per person aged 15 years or older¹.

Alcohol production and ingestion date back to 6000–9000 years ago. Alcohol has been used by most societies as a medication, for its psychotropic properties, and has been given a divine entity by some civilisations. However, ancient literature is also notable for warnings against excessive alcohol use.

Contemporary studies have shown the effects of alcohol on health depend on the amount and pattern of drinking. Mild to moderate alcohol consumption have been associated with cardioprotective properties and decreased all-cause mortality, whereas bingeing and abuse lead to detrimental effects on cardiovascular (CV) and overall health. The now well-recognised J-shaped relationship between alcohol consumed and all-cause mortality is shown in Figure 1².

According to the WHO, alcohol use is responsible for 2.5 million deaths annually and is the leading risk factor worldwide for death among males between 15 and 59 years of age. The majority of these deaths are attributed to accidents, violence and CV diseases¹. The adverse effects of alcohol on the CV system are manifested as cardiomyopathy, heart failure, stroke, arrhythmias and sudden cardiac death²⁻⁹. In this review, we will discuss the effects of alcohol and drinking patterns on the heart rhythm and its role in the pathophysiology of arrhythmogenesis.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies

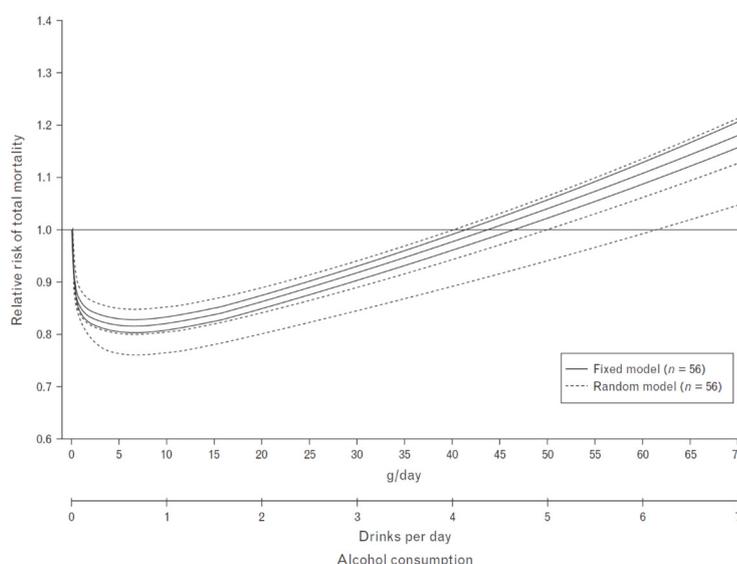


Figure 1: Relationship of amount of alcohol consumption and relative risk of all-cause mortality. Reprinted with permission from Di Castelnuovo et al.²

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have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Alcohol and atrial fibrillation

The association between alcohol and abnormalities of the heart rhythm and conduction system has been recognised since at least the mid-20th century. In a case series of 20 consecutive male patients with 'alcoholic heart disease' from the London Hospital in 1959, Evans reported the presence of extrasystoles, transient bundle branch block, atrial fibrillation or atrial tachycardia in 12 patients¹⁰. These findings were reproduced by Brigden and Robinson in 1964¹¹.

Ettinger and colleagues introduced the term 'holiday heart' in 1979 to describe the association of excessive alcohol intake between Thanksgiving and New Years with acute rhythm or conduction abnormalities, in the absence of underlying structural heart disease¹². Atrial fibrillation was the most commonly observed abnormality, followed by atrial flutter, ventricular or atrial premature complexes and paroxysmal atrial tachycardia. Significant electrolyte abnormalities were only present in a small percentage of patients and thus, the arrhythmias were attributed to cardiomyocyte toxicity during celebratory binge drinking.

In a case series of 41 patients with new onset atrial fibrillation, Lowenstein et al.¹³ reported that alcohol intoxication was present in 35% of patients. Excessive alcohol intake was the most commonly encountered etiological or contributing factor in patients younger than 65 years. Interestingly, in approximately 90% of cases, spontaneous conversion to normal sinus rhythm was observed within 24 hours.

In a single centre case-control study, Koskinen et al.¹⁴ reported that excessive alcohol intake was present in 15% – 30% of patients with idiopathic atrial fibrillation, prompting the authors to conclude that alcohol is a major etiological factor. Interestingly, no association between alcohol intake and recurrence of atrial fibrillation or development of chronic atrial fibrillation was observed in 4-year follow-up of the cohort¹⁵.

Data from large prospective cohort studies have addressed the relationship between chronic alcohol intake and atrial fibrillation. The Cardiovascular Health Study assessed the incidence of new onset atrial fibrillation among 5201 subjects aged 65 years and older during a 3-year follow-up. Most subjects used alcohol in moderation (average alcohol consumption of less than 3 drinks/week). Possibly because of this moderation, Psaty and colleagues¹⁶ found that alcohol use was associated with a reduced risk of atrial fibrillation.

Long-term (>25 years) follow-up of 10,333 participants of the Framingham study by Djousse et al.¹⁷ revealed non-significant effects of mild to moderate alcohol consumption on the incidence of atrial fibrillation. However alcohol consumption of greater than 36 g/day (approximately 3 drinks per day) was associated with a 34% increased risk of atrial fibrillation.

Frost and Vestergaard¹⁸ analysed data from approximately 48,000 subjects enrolled in the Danish Diet, Cancer and Health Study. After adjusting for traditional risk factors, alcohol use greater than 20 g/day (one drink = 15 g/day) was associated with an increased risk of atrial fibrillation or flutter among men, but not among women. These associations were independent of the pattern of drinking and the type of alcoholic beverage consumed. Overvad et al.¹⁹ used data from the same

cohort study to determine the effect of alcohol consumption on the prognosis of patients with atrial fibrillation. They concluded that excessive alcohol intake (defined as >27 drinks/week in men and >20 drinks/week in women) was associated with higher risk of thromboembolic events and increased mortality when compared with non-drinkers or light drinkers.

Mukamal et al.²⁰ studied the relationship between alcohol intake and incidence of atrial fibrillation among 16,415 Danes enrolled in the Copenhagen City Heart Study. A higher incidence of atrial fibrillation was observed among men consuming more than 35 drinks per week, whereas at lower levels of alcohol intake the relationship was flat. The authors could not draw safe conclusions about the female participants, as none consumed more than 28 drinks per week.

As these prior studies were underpowered to assess the relationship between alcohol consumption and atrial fibrillation in women, Conen et al.²¹ analysed data from the Women's Health Study, a cohort of 37,415 healthy middle-aged women. Participants were asked about their quantity of alcohol consumed and were followed for a median of 12 years. Consumption of two or more alcoholic drinks per day was associated with an increased risk of atrial fibrillation, whereas lesser alcohol intake did not increase risk.

Using data from more than 700,000 participants in the General Practice Research Database in the United Kingdom, Ruigomez et al.²² reported the incidence of chronic atrial fibrillation at 17 per 1000 person-years. Excessive alcohol intake (defined as consumption greater than 42 drinks per week) was an independent prognostic factor for chronic atrial fibrillation.

Two recent meta-analyses^{23,24} tested the hypothesis of a dose-response relationship between alcohol

consumption and development of atrial fibrillation. While the results of both meta-analyses showed that such a relationship does exist, the conclusions about the impact of light alcohol consumption were different. Samokhvalov et al.²⁴ reported that there is insufficient evidence regarding the impact of light drinking and that there may be a threshold under which there is no significant increase in the risk of atrial fibrillation. Conversely, Kodama et al.²³ interpreted the dose-response relationship as linear and not as J-shaped (Figure 2). Thus, even light alcohol consumption was associated with an increased risk of atrial fibrillation. In addition, Samokhvalov and colleagues characterised the relationship as causal, while Kodama and colleagues stated that more information is needed before such a conclusion can be drawn.

Alcohol and other supraventricular arrhythmias

Less data exist concerning the relationship between alcohol and supraventricular arrhythmias other than atrial fibrillation. As reported above, Ettinger and colleagues¹² found that in addition to atrial fibrillation, atrial flutter and paroxysmal atrial tachycardia were part of the 'holiday heart' syndrome.

In a small case-control study of 99 middle-aged patients presenting with supraventricular arrhythmias other than atrial fibrillation, Koskinen and Kupari²⁵ reported no significant difference in recent alcohol intake compared with matched controls. Conversely, Cohen et al.²⁶ found a statistically significant relationship between heavy alcohol consumption (defined as ≥ 6 drinks/day) and development of all supraventricular tachycardias.

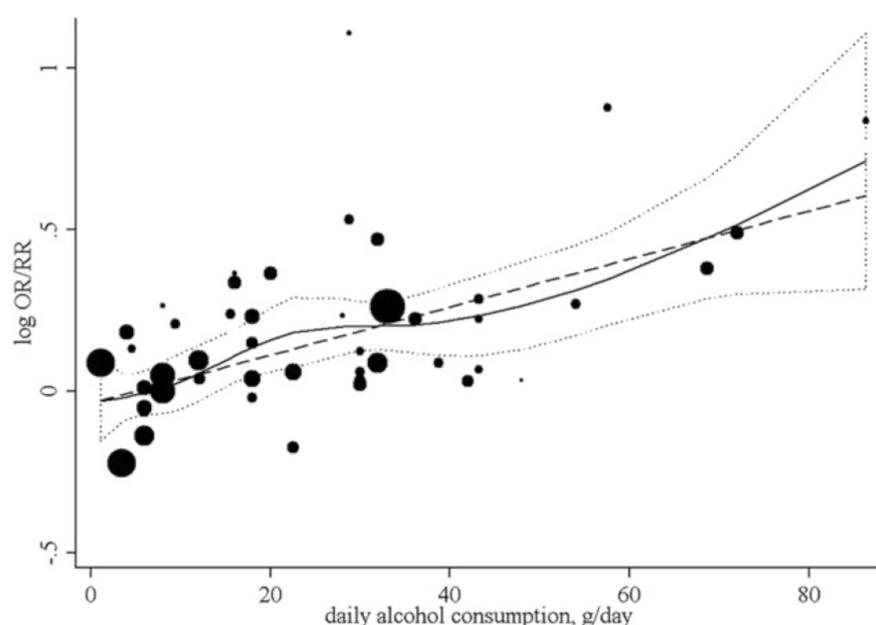


Figure 2: Regression of natural log OR/RR for atrial fibrillation on daily alcohol consumption. The solid curve and its accompanying area indicate the log odds ratio or relative risk (OR/RR) and its corresponding 95% confidence interval based on a restricted cubic spline regression model with knots at 8, 22.5 and 33.1 g/day of alcohol consumption. This model did not significantly improve the fit compared with the linear regression model expressed by the dotted line. The area of each data point is proportional to its statistical weight. Reproduced with permission from Kodama et al.²³.

In a recent case-control study of 195 consecutive patients with atrial fibrillation or atrial flutter, Marcus et al.²⁷ described a significant association between alcohol intake and development of atrial flutter in patients under 60 years of age (Table 1). Interestingly, the same study failed to show an association between alcohol consumption and atrial fibrillation.

Alcohol and ventricular arrhythmias or sudden cardiac death

In a case report by Singer and Lundberg in 1972, a 43-year-old alcoholic man admitted with syncope while drinking vodka was noticed to have runs of non-sustained ventricular tachycardia and frequent premature ventricular complexes²⁸. As no apparent aetiology of the syncope was found, he was given vodka with reproduction of the above arrhythmias. When vodka was administered while the patient was also receiving quinidine, suppression of the arrhythmias was observed.

More than a decade later, Panos et al.²⁹ reported induction of ventricular fibrillation with ethanol infusion in an alcoholic man admitted with aborted sudden cardiac death. The patient did not have underlying heart disease and his baseline electrophysiological study was normal. Unfortunately, the patient died 3 months later following heavy beer consumption.

Wannamethee and Shaper³⁰ analysed data from 7735 middle-aged men enrolled in the British Regional Health Study to assess the relationship between alcohol intake and sudden cardiac death (Figure 3 and Table 2). In a multivariate analysis, heavy alcohol consumption (more than 6 drinks per day) was associated with an increased (1.73) relative risk of sudden cardiac death.

Phillips et al.³¹ reported a higher incidence of sudden cardiac death during the Christmas and New Year's

Table 1 Odds ratios for the presence of atrial flutter (of all ages) for each progressive frequency of alcohol intake compared with 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

Holiday using the United States National Center for Health Statistics database. This was attributed, in part, to increased alcohol consumption during this period.

Albert et al.³² studied the effect of alcohol consumption on sudden cardiac death in men utilising data from the Physicians Health Study, where 21,537 male physicians were followed for a mean of 8 years. They found a U-shaped relationship, with the incidence of sudden cardiac death lowest among participants consuming 2–6 drinks/week. Chiuve et al.³³ observed the same U-shaped relationship between alcohol intake and sudden cardiac death in women based on data from the Nurses' Health Study, a prospective cohort study that enrolled 85,067 healthy women. The nadir in sudden cardiac death was observed with alcohol consumption of 5–14.9 g/day.

Mechanisms of arrhythmogenesis: intoxication

The mechanisms by which alcohol consumption predisposes to development of arrhythmias are multiple (Figure 4). Nutritional abnormalities, especially hypomagnesaemia and hypokalaemia, often encountered in alcoholics, are well known to be associated with development of arrhythmias³⁴.

Electrophysiological studies have demonstrated increasing levels of

alcohol consumption to be associated with decreasing right atrial effective refractory periods²⁷. Shortened atrial effective refractory periods provide a mechanism for development of atrial fibrillation and flutter^{27,35}. Heavy alcohol consumption has also been associated with decreased heart rate variability³⁶ and decreased vagal tone³⁷, factors known to be associated with tachyarrhythmias.

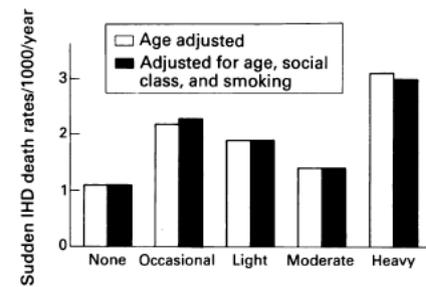


Figure 3: Alcohol intake and sudden death rates/1000/year, adjusted for age and in addition for social class and smoking. Reprinted with permission from Wannamethee and Shaper³⁰.

Day et al.³⁸ showed that patients with alcoholic cirrhosis and structurally normal hearts had prolonged QTc intervals when compared with controls. The 3-year follow-up revealed that this prolonged QTc interval was an independent risk factor for sudden cardiac death. Akamatsu et al.³⁹ found that individuals deficient in aldehyde dehydrogenase-2, an enzyme important in alcohol metabolism,

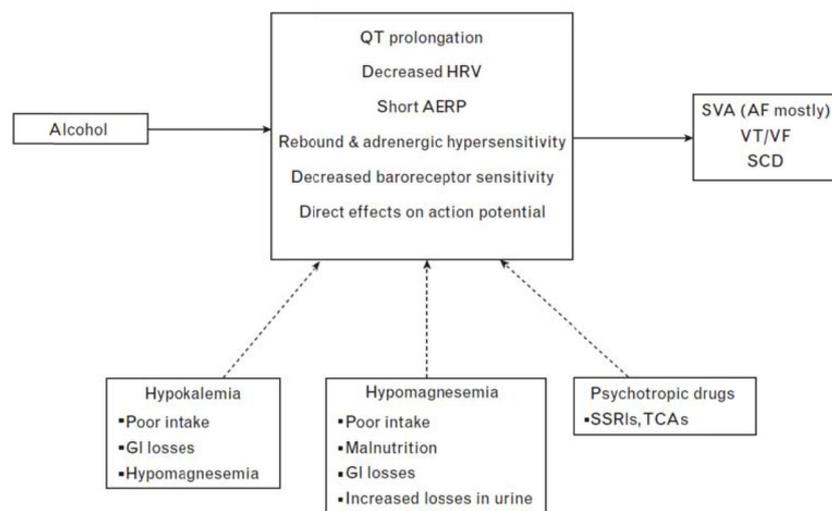


Figure 4: Possible pathophysiologic mechanisms of alcohol-induced arrhythmias. AERP, atrial effective refractory period; AF, atrial fibrillation; GI, gastrointestinal; HRV, heart rate variability; SCD, sudden cardiac death; SSRI, selective serotonin reuptake inhibitor; SVA, supraventricular arrhythmia; TCA, tricyclic antidepressant; VF, ventricular fibrillation; VT, ventricular tachycardia. Reproduced with permission from George and Figueredo³⁴.

Table 2 Alcohol intake and crude rate/1000/year for all deaths from IHD sudden and non-sudden IHD death and proportion of IHD deaths manifest as sudden in men with and without pre-existing IHD (numbers in parentheses are deaths. IHD, ischaemic heart disease. Reprinted with permission from Wannamethee and Shaper³⁰

Alcohol intake	No of men	All IHD deaths rate/1000	Sudden	Non-sudden	Percentage sudden	Age adjusted sudden death rate 1000 yr
No evidence of IHD						
None	320	1.2(3)	0	1.2(3)	0	0
Occasional	1379	2.5(26)	1.1(12)	1.4(14)	46.2%	1.1
Light	1953	2.1(33)	1.0(15)	1.1(18)	45.5%	0.9
Moderate	1534	1.5(18)	0.8(10)	0.7(8)	55.6%	0.8
Heavy	602	2.3(11)	1.9(9)	0.4(2)	81.8%	2.0
Total	5788	2.0(91)	1.0(45)	1.0(45)	50.5%	
Evidence of IHD						
None	146	11.1(13)	4.3(5)	6.8(8)	38.5%	4.0
Occasional	466	9.9(37)	5.6(21)	4.3(16)	56.8%	5.6
Light	491	8.9(42)	5.1(24)	4.3(16)	57.1%	4.0
Moderate	508	4.9(20)	2.7(11)	2.2(9)	55.0%	2.8
Heavy	230	7.6(14)	5.4(10)	2.2(4)	71.4%	5.8
Total	1941	8.1(126)	4.6(71)	3.5(55)	56.3%	

were more susceptible to QTc prolongation following alcohol intake.

Chen and colleagues⁴⁰ were able to demonstrate the proarrhythmic effect of alcohol on sinoatrial node preparations derived from rabbit hearts. They demonstrated this proarrhythmic effect was mediated through the hyperpolarisation-activated cyclic nucleotide-gated transmembrane ion channel. Using an animal model, Piano et al.⁴¹ demonstrated a direct cardiotoxic effect of alcohol on cardiac cells. Atrial muscle isolates from control rats and rats that had consumed alcohol for 2 months were stimulated with isoproterenol and primobendan. Tissue from rats that had consumed alcohol exhibited less inotropic response.

Eagle⁴² proposed the hypothesis that inhibition of sulphotransferase 1A1 due to phenolic compounds found in some alcoholic beverages can lead to malignant arrhythmias. Natural phenols and polyphenols,

found in alcoholic beverages such as red wine and dark beers, have been shown in *in vitro* studies to inhibit sulphotransferase 1A1, which decreases circulating free catecholamines. Therefore, heavy consumption may lead to a hyperadrenergic state and subsequently to malignant arrhythmias.

Mechanisms of arrhythmogenesis: withdrawal

Acute cessation of chronic alcohol intake may also lead to clinically significant disturbances of heart rhythm. Sinus tachycardia is common and constitutes one of the major diagnostic criteria of alcohol withdrawal syndrome⁴³. Supraventricular tachycardias are frequent and respond well to treatment with beta adrenergic blockers⁴⁴.

Fisher and Abrams⁴⁵ in 1977 reported a case of ventricular tachycardia and ventricular fibrillation in a patient hospitalised with alcohol

withdrawal syndrome and delirium tremens. Post resuscitation, the patient was treated with aggressive electrolyte (potassium and magnesium) repletion and antiarrhythmic medications. Ventricular arrhythmias in this setting have been linked to QTc prolongation, which is found in 40%–65% cases of patients with alcohol withdrawal^{46,47}.

Liu and Fujimiya were able to reproduce a hyperadrenergic state in rats with abrupt cessation of alcohol liquid diet. These study animals were shown to be more susceptible to sudden cardiac death when compared with animals with continuous alcohol intake. The risk returned to baseline 21 days post-alcohol cessation⁴⁸.

Conclusion

Epidemiological, animal and human intervention studies suggest alcohol consumption has both beneficial and detrimental effects on

CV health. While light to moderate alcohol consumption can produce cardioprotective effects, bingeing and abuse can lead to cardiomyopathy, heart failure, strokes, arrhythmias and sudden cardiac death. 'Holiday heart' due to supraventricular arrhythmias (mostly atrial fibrillation) and sudden cardiac death due to ventricular tachycardia and fibrillation are well-recognised sequelae of bingeing and heavy alcohol consumption. There appear to be a plethora of mechanisms underlying alcohol-induced arrhythmias, including electrolyte abnormalities, rebound and adrenergic hypersensitivity, QT interval prolongation, decreased heart rate variability and atrial effective refractory period, and more. Clearly, the only advice that can be given to any patient suffering an alcohol-induced arrhythmia at this time is abstinence and a healthier lifestyle.

Abbreviations list

CV, cardiovascular; WHO, World Health Organization.

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