27
Sudden Cardiac Death and Alcohol

Vincent M. Figueredo and Bhaskar Purushottam

Abstract

Alcohol is a well-recognized risk factor for sudden death. Alcohol abuse may contribute to a significant proportion of non-coronary sudden deaths. There are several mechanisms through which alcohol abuse could increase sudden death risk, including increasing the QT interval, decreasing vagal input, sympathoadrenal stimulation, electrolyte abnormalities and cardiomyopathy. Ventricular arrhythmias are the most common mode of alcohol-related sudden death, including automaticity, triggering and re-entry mechanisms. Other less common causes of alcohol-related sudden death including intracranial bleeds, heart blocks, metabolic acidosis with cardiac standstill, and exsanguinating gastrointestinal bleed, should be borne in mind, when evaluating an alcoholic patient who has been resuscitated.

Keywords

Alcohol • Alcohol abuse • Ethanol • Sudden death • Sudden cardiac death • Cardiomyopathy • Ventricular tachycardia • Withdrawal • Intoxication

Introduction

The consumption of alcoholic beverages has been documented as early as 10,000 BC [1]. Alcohol (French alcool/; Arabic al-kuhl) refers to the intoxicating constituent of wine, beer, spirits, or any of numerous beverages consumed in almost all societies; that is ethanol or ethyl alcohol (C2H5OH) [2]. As most cultures throughout history have consumed alcohol, either for social, religious or medicinal reasons, the potential abuse of and addiction to alcohol have long been recognized. Alcohol abuse contributes to 4 % of the global burden of disease [3].

In the United States, regardless of sex or race, long-term heavy alcohol consumption is the leading cause of non-ischemic cardiomyopathy [4]. There are approximately 79,000 deaths attributable to excessive alcohol use each year in the United States (US) [5]. This makes alcohol abuse the third leading lifestyle-related cause of death [6]. Alcohol abuse is responsible for 2.3 million years of potential life lost annually [7]. In the single year 2005, there were more than 1.6 million hospitalizations [7] and more than four million emergency room visits

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[8] for alcohol-related conditions. According to the Behavioral Risk Factor Surveillance System (BRFSS) survey, more than half of the adult US population drank alcohol in the past 30 days. Approximately 5 % drank heavily, and 15 % binge drank [9].

Each year, 300,000 cases of out-of-hospital cardiac arrest occur in the US [10]. Among the non-coronary causes of sudden cardiac death (SCD), alcohol is an important etiology. There are no consistent data on the proportion of SCD related to alcohol. One study postulated that as many as 5–50 % of SCD were attributable to alcohol [11]. Due to the limited data on alcohol consumption in most patients suffering cardiac pathologies, the role of alcohol as a cofactor in SCD may be underestimated.

Metabolism

Following oral administration, ethanol is absorbed rapidly into the bloodstream from the stomach and small intestine. Peak alcohol blood levels occur approximately 30 min after ingestion [12]. Gastric metabolism of ethanol is lower in women than in men, which may contribute to the greater susceptibility of women to ethanol [13, 14].

Ethanol is metabolized largely by sequential hepatic oxidation, first to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetic acid by aldehyde dehydrogenase (ALDH) [12]. The hepatic cytochrome P450 isozyme CYP2E1, can also contribute to ethanol metabolism, especially at higher ethanol concentrations and under conditions such as alcohol abuse, where its activity may be induced. Although CYP2E1 is not a major factor in ethanol metabolism, it can be an important site of interaction between ethanol and other drugs. During acute alcohol consumption there can be decreased clearance of CYP2E1 substrates that ethanol competes with for oxidation by the enzyme system (e.g., phenytoin and warfarin) [12]. The complex metabolism of ethanol along with genetic polymorphisms (e.g., ADH) may contribute towards differential susceptibility to SCD related to alcohol.

Effects of Alcohol on the Cardiovascular System

Cardioprotective Effects

In most countries, the risk of mortality due to coronary heart disease (CHD) is correlated with high dietary intake of saturated fat and elevated serum cholesterol levels. France is an exception to this rule, with relatively low mortality from CHD despite the consumption of high quantities of saturated fats; the "French paradox". Epidemiological studies suggest that widespread wine consumption may confer a cardioprotective effect, with one to three drinks per day resulting in a 10–40 % decrease in the risk of CHD events, compared to no alcohol consumption. In contrast, daily consumption of greater amounts of alcohol leads to an increased incidence of non-coronary causes of cardiovascular events, such as arrhythmias, cardiomyopathy and hemorrhagic stroke, offsetting the beneficial effects of alcohol on CHD; that is, alcohol has a J-shaped dose-mortality curve. Reduced risks for CHD are seen at average intakes as low as two to seven drinks per week [15]. Data based on a number of prospective, cohort, cross-cultural, and case–control studies in diverse populations consistently reveal lower rates of angina pectoris, myocardial infarction, and peripheral artery disease in those consuming light (1–20 g/day) to moderate (21–40 g/day) amounts of alcohol [12].

One possible mechanism by which alcohol could reduce the risk of CHD is through its effects on cholesterol. Changes in plasma lipoprotein levels, particularly increases in high-density lipoprotein (HDL) and decreases in low-density lipoprotein (LDL), have been associated with the protective effects of ethanol, regardless of the type of alcoholic beverage. Flavonoids found in red wine (and purple grape juice) may have an additional antiatherogenic role by protecting LDL from oxidative damage.

Another way in which alcohol consumption conceivably could play a cardioprotective role is by altering factors involved in clotting. Alcohol consumption elevates levels of tissue plasminogen activator, decreasing clot formation.

Decreased fibrinogen concentrations observed following ethanol consumption may also be cardioprotective [16]. Epidemiological studies have linked moderate consumption of ethanol to inhibition of platelet activation [17].

Pathological Effects of Alcohol on the Cardiovascular System

Hypertension

Consumption of greater than 30 g alcohol per day (more than two standard drinks) is associated with a 1.5–2.3 mm Hg rise in diastolic and systolic blood pressures [12]. Studies demonstrate a positive, nonlinear association between alcohol and hypertension [12]. The prevalence of hypertension attributable to excess alcohol consumption is not known, but studies suggest 5–11 % [12].

Cardiac Arrhythmias

Alcohol has pharmacological effects on cardiac conduction, including prolongation of the QT interval, prolongation of ventricular repolarization, and sympathetic stimulation [12]. Ventricular tachycardia may be responsible for the increased risk of unexplained SCD that has been observed in persons who are alcohol-dependent [18]. Atrial arrhythmias associated with chronic alcohol use include atrial fibrillation, atrial flutter, and supraventricular tachycardias. Fifteen to twenty percent of idiopathic cases of atrial fibrillation may be related to alcohol [19]. During continued alcohol use, treatment of these arrhythmias may be more resistant to cardioversion or medical therapy. Patients with recurrent or refractory atrial arrhythmias should be questioned carefully about alcohol use.

Cardiomyopathy

Alcohol has dose-related toxic effects on both skeletal and cardiac muscle. Numerous studies have shown that alcohol depresses cardiac contractility and can lead to cardiomyopathy [12]. Approximately half of patients with idiopathic cardiomyopathy in developed countries are thought to be alcohol-related. Although the clinical signs and symptoms of idiopathic and alcohol-induced cardiomyopathy are similar, alcohol-induced cardiomyopathy may have a better prognosis if patients are able to stop drinking [12]. As 40–50 % of persons with alcohol-induced cardiomyopathy who continue to drink die within 3–5 years, abstinence remains the primary treatment.

Stroke

Clinical studies indicate an increased incidence of hemorrhagic and ischemic stroke in persons who drink more than 40–60 g alcohol per day [20]. Many cases of alcohol-related stroke follow binge drinking episodes, especially when stroke occur in younger patients.

Epidemiological Data Regarding Alcohol Consumption and SCD

It is now well-known that alcohol consumption is one of the major modifiable risk factors in SCD – be it coronary or non-coronary in origin. One of the first studies to demonstrate an association between heavy alcohol use and SCD was published in 1977 by Dyer et al. [21]. In their study, 'problem drinkers' from the Chicago Peoples Gas Company had significantly higher 15-year mortality rates from all causes, cardiovascular diseases, coronary heart disease, and sudden death. These differences could not be entirely explained by their blood pressure, smoking, and relative weight status.

Wannamethee and Shaper [22] conducted a prospective cohort study (British Regional Heart Study) on 7,735 men, aged between 40 and 59 years, across 24 towns in England, Wales and Scotland in 1992. They found a positive association between drinking and the risk of SCD. As shown in Fig. 27.1, heavy drinkers had a nearly twofold increase in risk when compared to non-drinkers, even after adjusting for multiple confounding factors. Also noted in the study was that death from ischemic heart disease was more likely to be sudden in heavy drinkers.

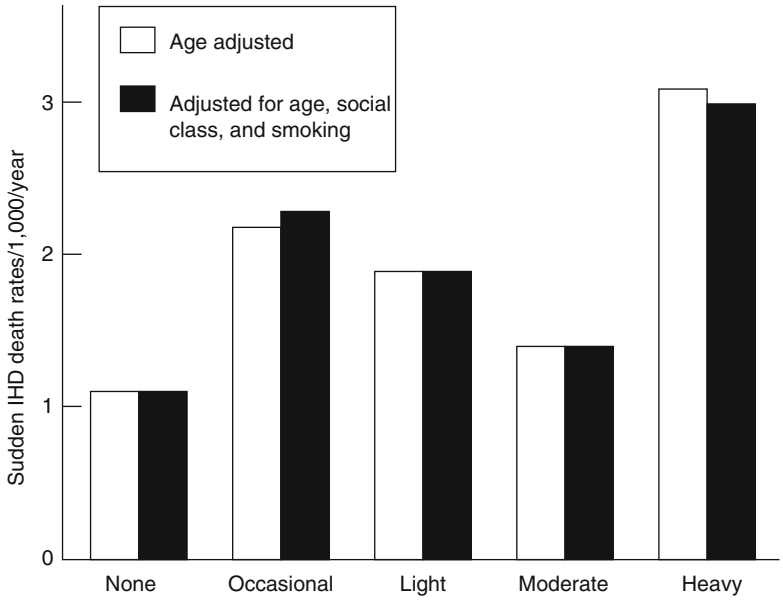

Figure 27–1. Alcohol intake and sudden death rates/1,000/year adjusted for age and in addition for social class and smoking (From Wannamethee and Shaper [22]. Reprinted with permission from BMJ Publishing Group)

Lithell et al. [23] prospectively followed 2,322 participants and 454 non-participants (50 year old men) for 10 years after a health screening examination in Uppsala, Sweden. Among the participants, 26 suffered sudden death and of those 46 % were registered with the Swedish temperance board (persons with heavy alcohol abuse, drinking offence or driving under the influence). In logistic analysis, persons registered with the temperance board had a significant high risk for SCD (odds ratio of 2.43).

Fraser and Upsdell [24], in the Auckland Study, compared definite myocardial infarction patients not dying suddenly with cases of SCD. They found that heavy drinkers had a higher proportion of coronary events presenting as SCD. The Framingham Study [25] found that sudden death, in the absence of clinical evidence of coronary heart disease, was more common among men drinking more than 90 oz of ethanol per month.

Given the association between heavy alcohol consumption and SCD, additional studies examined the question as to whether light-moderate alcohol consumption had an impact on SCD. Albert et al. [26] prospectively followed 22,071 apparently healthy male physicians in the Physicians Health Study, who were 40–84 years old and had no history of myocardial infarction, stroke, transient ischemic attacks or cancer. At baseline and at 84 months of follow-up, seven possible response categories of alcohol consumption were recorded. Over 12 years of follow-up they found that men who consumed two to four drinks per week or five to six drinks per week at baseline had significantly reduced risks of SCD of 60 and 79 %, respectively, compared with those who rarely or never consumed alcohol. The relationship between alcohol consumption and SCD was U-shaped, with the risk approaching unity at approximately two drinks per day. On the contrary, one prospective study from Finland [27] reported a positive association between moderate alcohol intake (≥200 g/month, equivalent to three to five drinks/week) and SCD. Albert et al. [26] suspected that the pattern of drinking, heavy consumption at less frequent settings per week, which was probably uncommon in the Physicians Health Study, could explain these discrepant results.

Recently, Chiuve et al. [28] conducted a prospective cohort study with 87,067 women from the Nurses' Health Study, who were free of chronic disease, to assess the association between alcohol intake and risk of SCD. After 26 years of follow-up they found a U-shaped association between alcohol consumption and risk of SCD in age- and calorie-adjusted, as well as multivariate-adjusted, models (Fig. 27.2). The lowest risk of SCD occurred among women who consumed

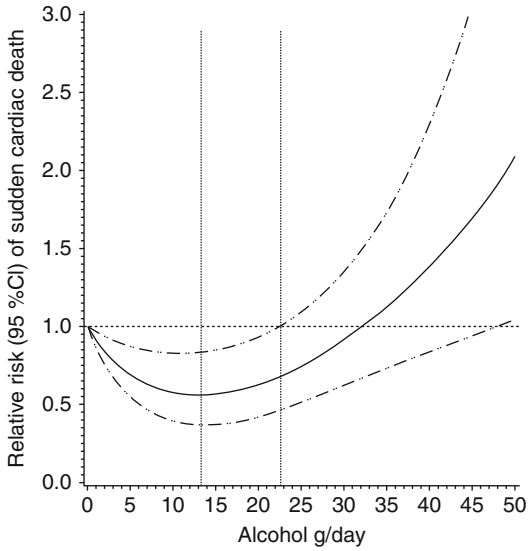

Figure 27–2. Multivariate relative risk of SCD as a function of alcohol intake data were fitted by a restricted cubic spline Cox proportional hazards model. The 95 % confidence intervals are indicated by the *dashed lines*. Models adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, physical activity and intake of omega-3 fatty acid, alpha-linolenic fatty acid, *trans*-fatty acid, ratio of polyunsaturated to saturated fatty acids, diagnosis of CHD, stroke, diabetes, high blood pressure and high cholesterol. The spline was based on 247 cases after the exclusion of former drinkers and women with intake >50 g/day (From Chiuve et al [28]. Reprinted with permission from Elsevier Limited)

5–14.9 g/day of alcohol (0.5–1 drink/day) when compared to abstainers (multivariate RR = 0.64). In women with the highest consumption of alcohol (>30 g/day) the multivariate RR was 1.15 when compared to the abstainers. Thus, epidemiological data from numerous studies suggest the risk of SCD to be lower in individuals with low to moderate alcohol intake (two to six drinks/week) compared with those who rarely or never consume alcohol or those with high intake (three to five drinks/day) and binge drinkers [2, 29].

Mechanisms of Sudden Cardiac Death Related to Alcohol

Evidence suggests a proarrhythmic milieu can develop in the settings of acute alcohol intoxication, alcohol withdrawal, and chronic alcohol abuse. Potential mechanisms of alcohol-induced arrhythmias are discussed below and are shown in Fig. 27.3.

Acute Alcohol Intoxication

Acute alcohol intoxication presents with central nervous system symptoms and signs after two to three drinks in most people (serum ethanol >50 mg/dL). Symptoms can range from euphoria to coma, depending on the alcohol level and associated drug use.

Alcohol ingestion causes an increase in the release of catecholamines [30, 31]. Perman [30] suggested that increased adrenaline excretion is due to adrenal medullary stimulation by ethanol. Howes et al. [31] demonstrated the dual effect of ethanol on increasing noradrenaline levels, as well as decreasing its clearance (the rise in noradrenaline commences 30 min after drinking and lasts for about 4 h). James and Bear [32] showed in anesthetized dogs that direct perfusion of the sinus node with acetaldehyde (metabolite of ethanol) produced significant stimulation of norepinephrine concentrations similar, to those occurring when humans consume alcohol.

Koskinen et al. [33] studied the acute effects of ethanol (dose of 1 g/kg body weight) on heart rate, blood pressure variability and baroreflex sensitivity in 12 healthy male subjects. They found a significant decrease in heart rate variability owing to diminished vagal modulation of the heart rate, reflecting reduced baroreflex sensitivity. Weise et al. [34] studied eight healthy volunteers and found that their blood pressure and heart rate remained unaltered during intoxication, but their heart rate variability was significantly reduced immediately after ingestion. Similarly, Rossinen et al. [35] demonstrated that in patients with coronary artery disease, acute ethanol intake elevated heart rate and reduced heart rate variability.

Aasebo et al. [36] studied 84 patients who were hospitalized with acute ethanol intoxication and found that P wave and QTc intervals were prolonged compared with sober subjects. Also, they found that P wave, PR, QRS and QTc intervals were longer when the subjects had high blood ethanol levels at admission than at discharge.

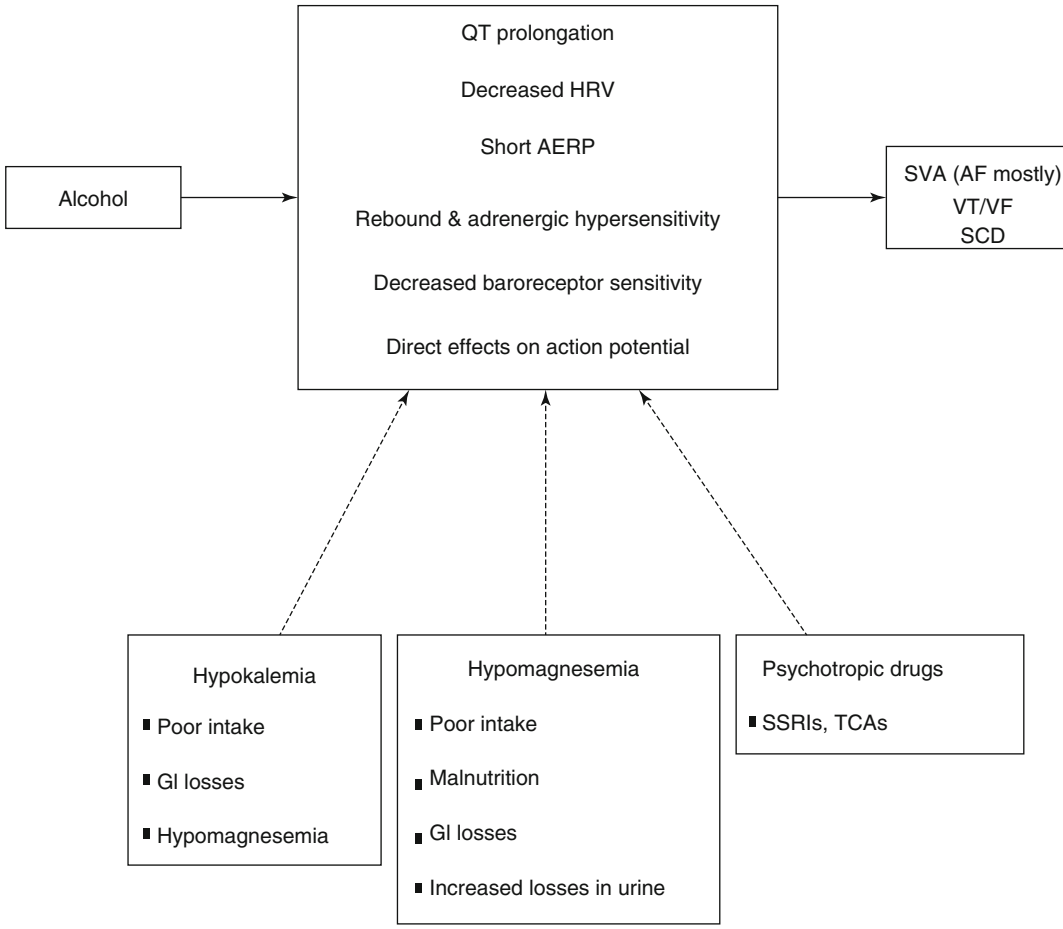

Figure 27–3. Potential mediators of alcohol-induced cardiac arrhythmias. *AERP* atrial effective refractory period, *AF* atrial fibrillation, *GI* gastrointestinal, *HRV* heart rate variability, *SCD* sudden cardiac death, *SSRI* selective serotonin reuptake inhibitor, *SVA* supraventricular arrythmia, *TCA* tricyclic antidepressant, *VF* ventricular fibrillation, *VT* ventricular tachycardia (From George and Figueredo [2]. Reprinted with permission from Lippincott Williams & Wilkins)

Further studies are needed to examine the role of QRS duration in alcohol-related SCD.

Buckingham et al. [37] studied 38 patients admitted to an acute community alcoholic detoxification center with 24-h ambulatory electrocardiograms and serum ethanol levels. They found a correlation between serum ethanol level and the mean rate of ventricular ectopic beats/h. Nonsustained ventricular tachycardia was more common in patients with previous underlying heart disease.

Animal experiments [38] have shown that high concentrations of ethanol produce concentration-dependent coronary vasospasm, which were not prevented by several antagonists. This could be another potential mechanism through which binge drinkers may develop SCD.

As delineated above, multiple potential mechanisms can predispose those with acute alcohol intoxication to life-threatening arrhythmias, including QT prolongation and increases in catecholamine levels.

Acute Alcohol Withdrawal

Acute alcohol withdrawal syndrome consists of symptoms and signs that include tremor, agitation, anxiety, and autonomic nervous system overactivity, manifested by increases in heart rate, respiratory rate, and body temperature.

Withdrawal usually begins 5–10 h after ethanol intake, peaks on day 2 or 3, and improves by day 4 or 5, although mild levels of these problems may persist for 4–6 months as a protracted abstinence syndrome. Approximately 2–5 % of alcoholics experience delirium tremens, where the withdrawal includes delirium (mental confusion, agitation, and fluctuating levels of consciousness) associated with a tremor and autonomic overactivity [39]. In this state of heightened activity, patients are at an increased risk for SCD.

Maki et al. [40] studied ten male subjects attending a withdrawal clinic after prolonged alcohol abuse. One day into withdrawal, there was a significant elevation of beta-adrenoceptor levels, which was accompanied by a parallel activation of the beta-adrenoceptor-mediated cAMP production of lymphocytes. There were no major changes in beta-adrenoceptor levels or cAMP production during the next 7 days. Interestingly, on admission the mean beta-adrenoceptor density was approximately 60 % of the mean level of healthy control subjects. Plasma catecholamine levels were elevated at arrival and decreased steadily during the withdrawal period. They concluded that chronic alcoholism is associated with a reduction of lymphocytic beta-adrenoceptor density and functioning, which is followed by a rapid reversal during withdrawal. Further, this is responsible for the accelerated heightened responsiveness to catecholamines during the first ethanol-free day of chronic alcoholics.

Bar et al. [41] investigated baroreflex sensitivity, heart rate variability, blood pressure variability, cardiac index, left ventricular work index and total peripheral resistance in 20 patients undergoing acute alcohol withdrawal, compared with matched controls. They found a marked down-regulation of baroreflex sensitivity during acute alcohol withdrawal. Non-linear parameters of heart rate variability and baroreflex sensitivity correlated with the severity of the acute alcohol withdrawal syndrome. Interestingly, they also found a milder down-regulation of baroreflex sensitivity in 15 abstaining alcoholics.

The QT interval reflects the most critical phase for the generation of reentry and ventricular arrhythmia generation [42]. Berger et al. [43] established a index normalizing QT variability to heart rate variability. Beat-to-beat QT interval variability reflects the temporal fluctuation in ventricular repolarization and provides a window into repolarization abnormalities [44]. Abnormal QT variability is associated with ventricular arrhythmias and SCD [45–47]. Bar et al., studied high resolution electrocardiographic recordings from 18 patients suffering from acute alcohol withdrawal, 18 matched controls and 15 abstaining alcoholics. They found that the heart rate and QT variability index were significantly increased in acute alcohol withdrawal. In contrast, abstained alcoholics did not significantly differ from controls.

Otero-Antón et al. [48] studied QT intervals in 62 patients (52 male; 10 female) who were admitted with acute alcohol abstinence syndrome. They found that 47 % had a prolonged QTc interval of more than 440 milliseconds on their admission ECG. In 27 patients, who had a second ECG during the hospital stay, the QTc interval had significantly shortened. Eight patients found to have prolonged QTc on admission had a second ECG performed on them after complete recovery from withdrawal symptoms and in all cases the QTc interval had returned to normal.

Cuculi et al. [49] performed a retrospective analysis on 49 patients (38 males, 11 females) with a diagnosis of delirium tremens or alcohol withdrawal seizures. The QTc interval was prolonged in 63 %, with 10 % developing tachyarrhythmias (two torsade de pointes, one sustained ventricular tachycardia, two supraventricular tachycardias, and one atrial fibrillation).

Electrolyte abnormalities are commonly present during withdrawal in chronic alcohol abusers [50–53], which can increase arrhythmia risk [54]. Stasiukyniene [55] studied 114 chronic alcoholics during withdrawal. Hypokalemia was observed in 29 %, hypomagnesemia in 30 %, and hyponatremia in 73 %. Potential causes include: poor nutritional intake and malabsorption; increased excretion during vomiting, diarrhea and diuresis; decreased renal tubular reabsorption; altered ionic permeability of cells; elevated plasma catecholamines and respiratory alkalosis (from hyperventilation) which cause an intracellular shift of potassium and magnesium [56]. The more pronounced the alcohol withdrawal syndrome, the sharper the decline in potassium

and magnesium levels [51], which in turn increases the risk for arrhythmias and SCD.

Animal experiments [57] have demonstrated that abrupt termination of an ethanol regimen provokes ventricular arrhythmias and enhances susceptibility to the arrhythmogenic effects of epinephrine. In summary, heightened catecholamine activity and effects on heart rate variability and baroreflex sensitivity, along with QT prolongation, may contribute towards SCD in acute alcohol withdrawal.

Chronic Alcohol Abuse

Alcohol dependence is defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as repeated alcohol-related difficulties in at least three of seven life areas that cluster together at about the same time. Alcohol abuse is defined as repetitive problems with alcohol in any one of four life areas—social, interpersonal, legal, and occupational—or repeated use in hazardous situations such as driving while intoxicated. In the US, in both sexes and all races, chronic alcohol abuse is the leading cause of non-ischemic cardiomyopathy [4]. There are several changes at the gross, histological and molecular levels that may contribute to increased SCD. To follow are studies which examine the association of chronic alcohol abuse and SCD, as well as the possible alcohol-related mechanisms of SCD.

Vikhert et al. [58] studied 752 SCD cases. Alcoholic cardiomyopathy was found in 17 %; predominantly in men under age the 50 (73 %). Gross morphology, light microscopy, electron microscopy and enzyme histochemistry findings were similar to other forms of dilated cardiomyopathy.

Kino et al. [59] found the most frequent cardiovascular finding in 145 asymptomatic male chronic alcoholics admitted to Ranryoen Hospital, Japan (alcohol detoxification centre) was a prolonged QTc interval of more than 440 milliseconds (43 %), unrelated to serum electrolyte abnormalities. Day et al. [60] prospectively followed 69 patients with histologically proven alcoholic liver disease (without evidence of structural heart disease, abstinent from alcohol for at least 7 days before investigation) and 40 healthy non-drinking controls, matched for age and sex. They found that QT intervals recorded at the start of the study were longer in alcoholics than in controls (unrelated to electrolyte abnormalities). Also, the QT intervals were prolonged in the 14 patients who died compared with survivors, mainly due to long QT intervals in the 6 patients with SCD (Fig. 27.4). Borini et al. [56] in a study from Brazil, found that 55 % of their 44 female alcoholics had a prolonged QTc interval.

Milovanovic et al. [61] studied 25 patients with alcoholic liver cirrhosis to analyze the risk predictors for SCD related to autonomic dysfunction. As shown in Fig. 27.5, based on autonomic reflex tests, these subjects had a high incidence (56 %) of severe autonomic dysfunction, manifested as pronounced vagal impairment. The presence of vagal neuropathy in liver cirrhosis is an independent predictor of mortality [62]. Other studies have shown that chronic alcohol ingestion is associated with autonomic neuropathy, predominately of vagal origin [63–65], potentially contributing to the increased incidence of SCD in alcoholics [66, 67]. Genovesi et al. [68] showed that the QT/RR slope was steeper in 48 cirrhotic patients with an alcoholic etiology when compared to those with a viral etiology.

Malpas et al. [69] performed autonomic function testing in 23 alcohol dependent men (changes in heart rate, RR interval and blood pressure with deep breathing, standing, Valsalva maneuver, neck suction) and measurement of 24 h heart rate variability, and compared them with 11 healthy men. Sixteen alcohol dependent men (group 1) had normal standard autonomic function tests and seven had vagal neuropathy (group 2). As shown in Fig. 27.6, the 24 h heart rate variability was significantly lower in both alcohol dependent groups than in controls, while the two alcohol dependent groups were not significantly different from each other. This could suggest that 24 h heart rate variability was more sensitive in detecting changes in autonomic integrity than the standard tests of autonomic function [69]. A similar pattern was seen in a previous study of diabetic patients [70].

Sakagami et al. [71], studied patients with alcoholic pancreatitis (n = 36) and alcoholic dependence (n = 37), and compared them to healthy control subjects (n = 36). They found that

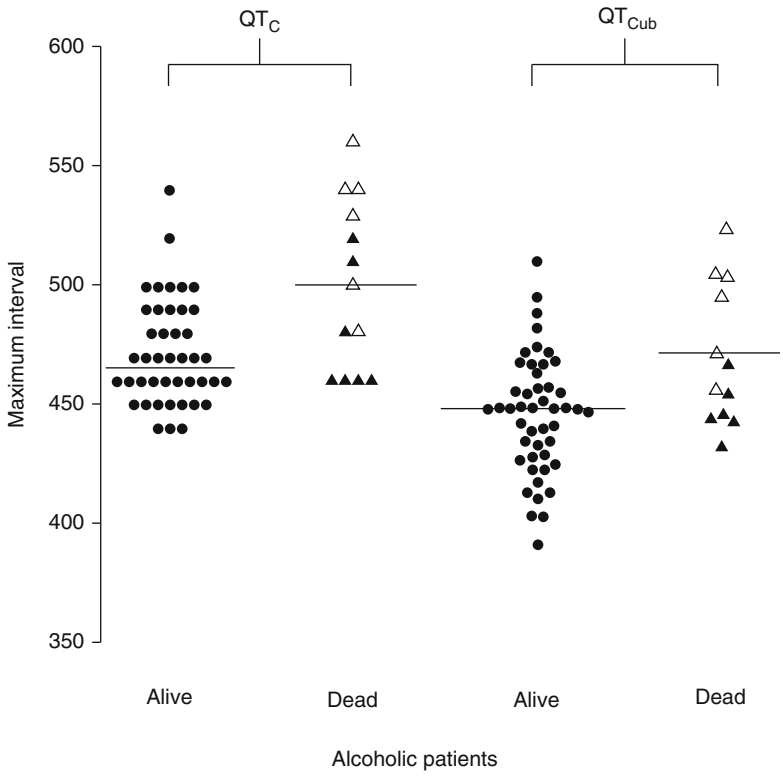

Figure 27–4. Corrected QT intervals in alcoholic patients and survival. *Open triangle* cardiac sudden death, *solid triangle* non-cardiac cause of death. *Horizontal lines* represent means (From Day et al. [60]. Reprinted with permission from Elsevier Limited)

patients with alcoholic pancreatitis and alcohol dependence had a longer QT and increased QTc dispersion compared to control subjects. Interestingly patients with alcoholic pancreatitis had a longer QT and increased QTc dispersion than those with alcoholic dependence only. Often, patients with alcoholic pancreatitis also have secondary diabetes and therefore a greater risk for autonomic dysfunction, which could explain the increased QT and QTc dispersion [63, 72, 73]. Whether this translates into a higher risk of SCD in the patients with alcoholic pancreatitis requires further study.

Chronic alcohol abuse can cause dilated cardiomyopathy with a dose-dependent decrease in left ventricular ejection fraction. Fauchier et al. [74, 75] studied 194 patients with non-ischemic dilated cardiomyopathy. When they compared 28 patients with alcoholic cardiomyopathy without abstinence with 119 patients with idiopathic cardiomyopathy, they found a similar event rate in SCD, sustained ventricular tachycardia and ventricular fibrillation during a mean follow-up of 51 months (Fig. 27.7). In contrast, patients with alcoholic cardiomyopathy who abstained (n = 47) had a significantly lower number of events when compared to the other groups, highlighting the importance of abstinence in alcohol-related cardiomyopathy.

In chronic alcohol abuse, the mode of SCD appears multifactorial. In addition to cardiomyopathy, prolonged QTc, increased QTc dispersion, steeper QT/RR slope and autonomic dysfunction with vagal impairment can all be contributing factors to SCD.

Electrophysiological Effects of Alcohol

One of the most quoted studies regarding the electrophysiological effects of alcohol in alcoholics is by Greenspon and Schal [76]. Fourteen patients with a history of rhythm disturbances, heart disease and alcohol abuse underwent electrophysiological testing at baseline (non-sedated state) and after 90 mL of 80-proof whiskey. One patient developed nonsustained ventricular tachycardia and another had paired ventricular

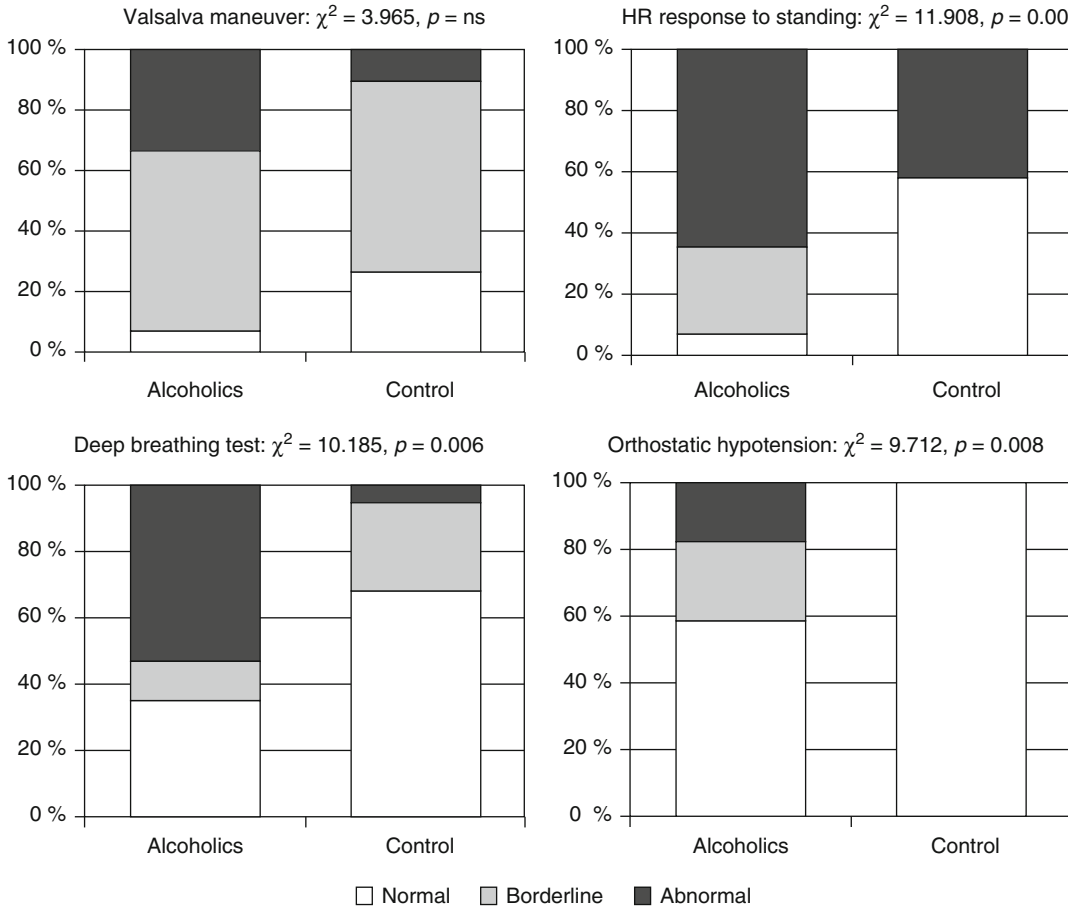

Figure 27–5. Cardiovascular reflex tests (From Milovanovic et al. [61]. Reprinted with permission from Institute of Molecular Physiology and Genetics)

responses. Post alcohol administration, one patient developed sustained ventricular tachycardia and four developed non-sustained ventricular tachycardia. The His-ventricle interval was observed to be increased post alcohol administration. One patient was admitted to the hospital with a Mobitz II block post alcohol administration.

Panos et al. [77] reported on a case of a binge drinker, who had been resuscitated from a cardiac arrest, and had normal baseline electrophysiological testing. Following intravenous alcohol administration, paired ventricular extrastimuli from a right ventricle pacing catheter induced a rapid polymorphic ventricular tachycardia requiring cardioversion. Repeat electrophysiological testing 24 h later in the absence of alcohol was again normal. Another study by Gould et al. [78, 79] found that ethanol alters conduction velocity and action potential duration, which can facilitate ventricular re-entry.

In vitro studies [80–82] suggest that high concentrations of alcohol can shorten the atrial and ventricular action potential durations. Studies in animal models [83] have demonstrated prolonged atrioventricular and intraventricular conduction times. Ettinger et al. [84] reported a decreased ventricular fibrillation threshold in chronic alcohol fed animals, which were given alcohol acutely. Similarly, Guideri et al. [85] found an increased sensitivity during withdrawal to ventricular arrhythmias and sudden death in animals that were pretreated with alcohol for 7 weeks.

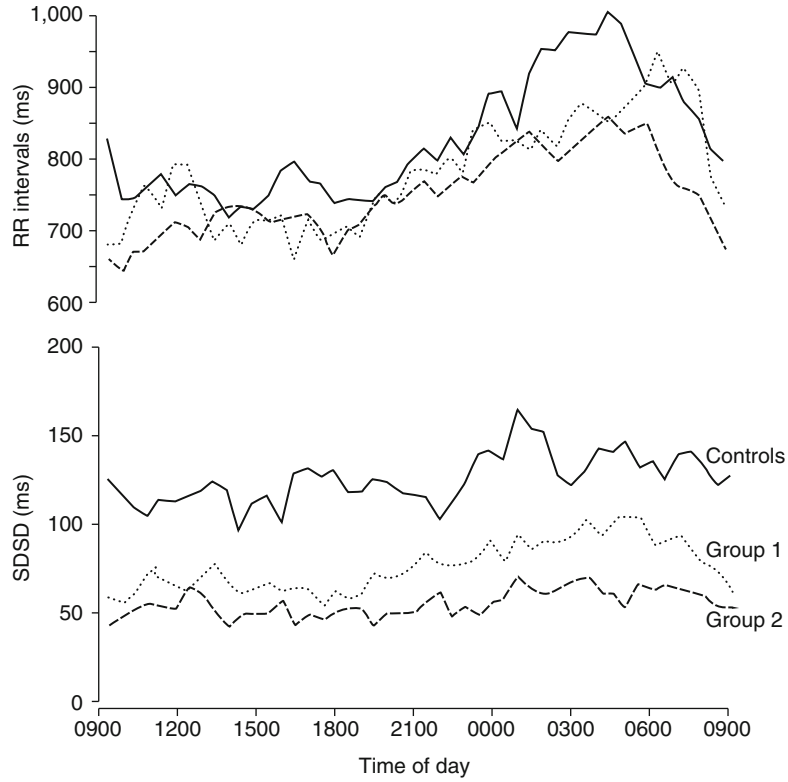

Figure 27–6. Individual mean heart rate variability (SDSD) in the three groups for the whole 24 h period. The *solid line* indicates the mean value in each group. There was a significant difference between controls and both alcohol dependent groups that the standard tests of autonomic function did not identify (From Malpas et al. [69]. Reprinted with permission from BMJ Publishing Group Ltd)

Klein et al. [86] were the first to show the acute inhibitory effects of alcohol on single cardiac sodium channel gating. Reduction of sodium channel activity can lead to an increased sodium-calcium-exchanger activity in the myocardium, which then prolongs the action potential; thus making the myocardium vulnerable to afterdepolarizations which can trigger ventricular arrhythmias [87]. This may be the mechanism through which QT interval is prolonged. However, additional studies are needed to establish this relationship.

Genetic Factors in Alcohol and Sudden Cardiac Death

Several genetic polymorphisms controlling alcohol metabolism have been identified [88]. These include ADH isoforms (ADH1A, 1B, and 1C), ADH1B gene polymorphisms, gamma-1 and gamma-2 forms of ADH1C, CYP2E1, CYPs1A2, CYP3A4, and ALDH2*2 [12]. A recent study demonstrating variations in susceptibility genes and their relation to dilated cardiomyopathy in chronic alcoholics found that only a fraction of patients actually develop dilated cardiomyopathy, which suggests a genetic vulnerability [89]. Similarly, there could be genetic factors which could influence inter-individual variation in myocardial electrophysiological responses to alcohol. This will require further study.

Other Things to Consider

As discussed earlier, electrolyte abnormalities during the acute alcohol withdrawal stage, such as hypokalemia and hypomagnesemia, can set up the substrate for life threatening

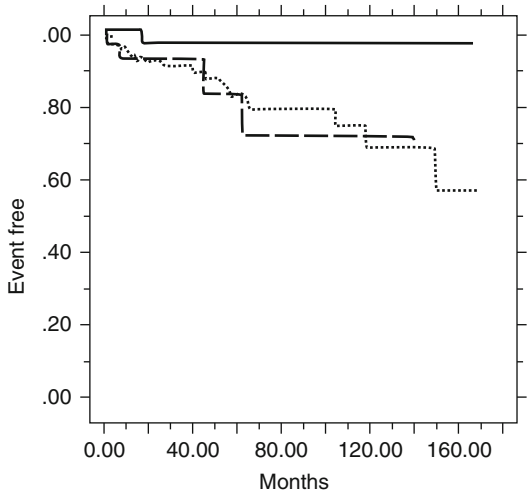

Figure 27–7. Survival curves of sudden deaths and major arrhythmic events (sustained VT, VF) in patients with ACM and IDCM. The *solid line* indicates patients with ACM and alcohol abstinence, the *small dashed line* indicates IDCM, and the *large dashed line* indicates patients with ACM without abstinence. Compared to patients with ACM and alcohol abstinence, relative risk of events was 8.0 for patients with ACM without abstinence (log-rank test, $p = 0.01$) and 7.3 for patients with IDCM (log-rank test, $p = 0.03$) (From Fauchier [74]. Reprinted with permission from American College of Chest Physicians)

ventricular arrhythmias. Alcoholic ketoacidosis occurs following prolonged excessive alcohol consumption, mainly due to starvation and glycogen depletion, fluid volume depletion and an elevated NADH/NAD rate secondary to alcohol metabolism, which in turn causes ketoacid generation. A severe form of this process results in severe metabolic acidosis, which can result in pulseless electrical activity. Yanagawa et al. [90] reported six cases of cardiac arrest in alcoholic ketoacidosis. All six exhibited pulseless electrical activity upon sudden cardiac arrest. Coronary thrombosis, pulmonary thrombosis, tension pneumothorax and cardiac tamponade were excluded. They concluded that severe metabolic acidosis with respiratory acidosis, hypoxia, hypothermia and hemorrhage contributed to the cardiac arrests.

Abusers of alcohol are more likely to abuse non-prescription drugs such as cocaine and amphetamines, which can result in life threatening arrhythmias and SCD (see Chap. 28). Alcoholics tend to have a higher incidence of psychiatric morbidity, often requiring medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors and lithium, which can prolong the QT interval. Alcohol can be a strong contributing factor in hemorrhagic strokes [11, 91, 92], which can be fatal if they are large in size or involve the brainstem region causing cerebral edema, herniation, ventricular arrhythmias, sudden vagotonic stimulation with bradycardia and cardiac standstill [93–96]. There have been a few case reports of alcohol induced sinus bradycardia [97] and Mobitz II block [77], which can cause syncope and may have the potential to cause sudden death. The probability of alcohol causing coronary vasospasm as suggested in one animal experiment [38] remains controversial.

Excessive alcohol consumption can cause severe, poorly controlled hypertension, a main cause of aortic dissection, which can lead to sudden death. While the etiologic link between excessive alcohol consumption and aortic dissection is highly plausible, it remains to be confirmed in large registries and studies [98]. Alcohol intoxication or withdrawal can result in status epilepticus [99–101], which has the potential to culminate into sudden death [102]. Finally, alcoholism is associated with trauma and exsanguinating gastrointestinal bleeding, both of which can lead to sudden death.

Management

Clearly, prevention is the best treatment. Patients should be educated about the hazards of excessive drinking. The judicious use of beta blockers, for antihypertensive and anti-catecholamine actions, fluids, benzodiazepines and correction of metabolic and electrolyte abnormalities in monitored settings are very important during acute intoxication and withdrawal stages. In alcoholic cardiomyopathy, treatment should follow the standard guidelines as advised for non-ischemic cardiomyopathy, with abstention.

As per the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines, complete abstinence from alcohol is recommended [29] (class

I recommendation with level of evidence C) in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias. It is a class I recommendation for implantable cardioverter-defibrillator (ICD) therapy in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes. Given the strong addiction with alcohol and the complex interactive mechanisms in SCD, it becomes an individualized decision in ICD therapy. Such matters require detailed discussions with the patient (and the family) with the single most important intervention being to avoid the offending agent. There is no data on the preemptive or prophylactic use of antiarrhythmic medications. Their use should be guided as per the clinical situation.

Conclusions

Alcohol is a well-recognized risk factor for SCD. Alcohol abuse may contribute to a significant proportion of non-coronary sudden deaths. There are several mechanisms through which alcohol abuse could increase SCD risk, including increasing the QT interval, decreasing vagal input, sympathoadrenal stimulation, electrolyte abnormalities and cardiomyopathy. Ventricular arrhythmias are the most common mode of alcohol-related SCD, including automaticity, triggering and re-entry mechanisms. Other less common causes of alcohol-related sudden death including intracranial bleeds, heart blocks, metabolic acidosis with cardiac standstill, and exsanguinating gastrointestinal bleed should be borne in mind, when evaluating an alcoholic patient who has been resuscitated. The current recommendations on alcohol intake are not to exceed >2 drinks/day for men and 1 drink/day for women with no underlying heart disease. It is advised to abstain from alcohol if a patient has cardiomyopathy. Despite the pervasive use of alcohol in most societies, much remains unknown regarding its electrophysiological effects of the myocardium and its influence on SCD.

Conflicts of Interests **None**

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