Observational Study

Medicine

OPEN

Sudden cardiac death in patients with coronary heart disease and antemortem alcohol intake

A STROBE – compliant retrospective study

Dmitrij Fomin, PhD[a], Sigitas Chmieliauskas, PhD[b,*], Sigitas Laima, PhD[b], Jurgita Stasiuniene, PhD[b], Algimantas Jasulaitis, PhD[b], Pranas Serpytis, PhD[a]

Abstract

The present study was aimed to assess the prevalence and possible causal relationship of alcohol intake prior to a sudden cardiac death event in patients with coronary artery disease. The retrospective research was performed at the Vilnius branch of The State Forensic Medicine Service. The autopsy protocols for five years were analyzed and the cases of sudden cardiac death were selected, when the determined cause of death was Coronary Heart Disease (CHD), a forensic autopsy and toxicological blood and urine test had been performed. Cases of the sudden death of non-cardiac origin, cases of cardiomyopathy of various origins, and cases of acute cardiac arrest of unspecified origin were excluded. The data collected was processed using R software. The study sample consisted of 2133 cases. 706 (33%) CHD cases were alcohol positive. Males and young age CHD victims were more likely to find alcohol than females (72% vs. 28%, respectively, $P < .001$). The mean blood alcohol concentration of the sample was 1.37 ‰± 1.01, urine's 1.73‰ ± 1.29. Alcohol was more commonly found during the winter months and the holidays. Deaths in alcohol-positive individuals were more common in the alcohol elimination phase with hemodynamically insignificant coronary artery stenosis (up to 50% of arterial lumen). Nearly every third CHD victim in Lithuania who experienced sudden death also had signs of antemortem alcohol consumption.

Abbreviations: CHD = Coronary Heart Disease, SCD = Sudden Cardiac Death.

Keywords: alcohol, coronary heart disease, forensic science, sudden death.

1. Introduction

Coronary heart disease (CHD) is the most common cause of sudden cardiac death in Lithuania. This affects not only older people but people of working age.[1] The standardized mortality rate for CHD working-aged men in Lithuania is the highest in the European Union.[2] Although morbidity and mortality from CHD in Lithuania are high, which is explained by unhealthy lifestyle and other natural causes, such high mortality from CHD suggests that the cause of death may be influenced by other factors. Several studies hypothesize that some of the sudden deaths from CHD may be related to the toxic effects of alcohol.[3,4]

Observational studies show that light-to-moderate consumption of alcohol is beneficial in relation to the risk for CHD.[5] Binge and heavy drinking are known to be harmful, and consumption of alcohol apart from meals is considered to be less favorable.[6] Also, alcohol consumption is a stick with two ends in relation to heart failure. Heavy drinkers have an increased risk of non-CHD-associated heart failure. On the contrary, alcohol consumption may protect against CHD-associated heart failure.[7] Chronic heavy drinking is known to increase the rate of sudden death, and sudden consumption of large amounts of alcohol can cause atrial fibrillation, increased ventricular ectopic activity, and tachyarrhythmias.[8–10] Acute alcohol consumption in CHD may increase electrical instability. Especially in the presence of factors such as myocardial ischemia and hypertrophy, the acute effects of alcohol can be very harmful.

Despite these arguments, population-based data on alcohol use before sudden cardiac death from CHD are rather limited. Therefore, we assessed blood and urine alcohol concentrations in sudden-onset CHD subjects who underwent forensic examinations at the Vilnius branch of the Lithuanian Forensic Medicine Service.

2. Methods

2.1. Study design and data source

There was performed a retrospective study of patients, whose cause of death was coronary heart disease. The research was

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Lithuania [b] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Lithuania.

**Correspondence: Sigitas Chmieliauskas, Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, M. K. Ciurlionio str. 21/27, Lithuania (e-mail: sigitas.chmieliauskas@mf.vu.lt).*

How to cite this article: Fomin D, Chmieliauskas S, Laima S, Stasiuniene J, Jasulaitis A, Serpytis P. Sudden cardiac death in patients with coronary heart disease and antemortem alcohol intake: A STROBE – compliant retrospective study. Medicine 2022;101:45(e31396).

Received: 9 March 2022 / Received in final form: 23 September 2022 / Accepted: 28 September 2022

http://dx.doi.org/10.1097/MD.0000000000031396

designed as a retrospective cohort study and was approved by the Ethics Committee of Vilnius regional biomedical research. The data, regarding postmortem investigation of the victims between 2016 and 2020 years was obtained from the Lithuanian State Forensic Medicine Service database. The data concerning the patients with coronary heart disease as the cause of death was collected from the central health e-database of Lithuania (www.esveikata.lt).

This Lithuanian health dataset included demographic data of the patients, diagnoses as well as information regarding the cause of death. All decedents received full autopsies. In all cases where there was blood and/or urine, a toxicological study was performed to determine the ethanol concentration. Alcohol levels in the blood or the urine were measured by gas chromatography. In every case, there was information provided from the law enforcement agencies, including the scene of the incident, time of death, and the presumable death mechanism.

2.2. Identification of cases

The study included cases of sudden cardiac death in which CHD was identified as the leading cause of death in death certificates. Forensic identification of death due to CHD was based on the following principles (Fig. 1) Sudden death was defined as death that occurred at witnesses within 6 hours of the onset of symptoms, or within 24 hours since the last time the person was feeling well. Cases of the sudden death of non-cardiac origin, cases of cardiomyopathy of various origins, and cases of acute cardiac arrest of unspecified origin were excluded based on the results of a complete autopsy, including toxicological studies.

Cases of CHD where acute myocardial infarction was diagnosed as a direct cause of death were selected as a control group.

2.3. Statistical analysis

The data collected was processed using R software. The Shapiro–Wilk test was used to determine whether the data was normally distributed. The Student's t-test was used to assess the statistical significance of differences of continuous variables between the study groups. The statistical significance of differences of categorical variables between the study groups was evaluated using the Chi-square test. Spearman's correlation coefficients were assessed. A weak correlation was defined as r–values < 0.39; a moderate correlation with r–values from 0.40 to 0.69; and a strong correlation with r–values > 0.70. In addition, 95% confidence intervals were calculated. Differences with P values less than 0.05 were considered significant.

3. Results

16,056 autopsies were performed at the Vilnius branch of VTMT from 2016 to 2020. During this period, 2133 (13.28%) cases of sudden cardiac death were diagnosed with CHD as the leading cause of death in death certificates. Ethyl alcohol was found in the blood of almost a third of the sample, 29.5% (n = 630). Depending on the time that has elapsed since the last episode of alcohol consumption and death, some part of the alcohol is already excreted by the kidneys from the blood into the urine. Using blood or urine alcohol levels, whichever

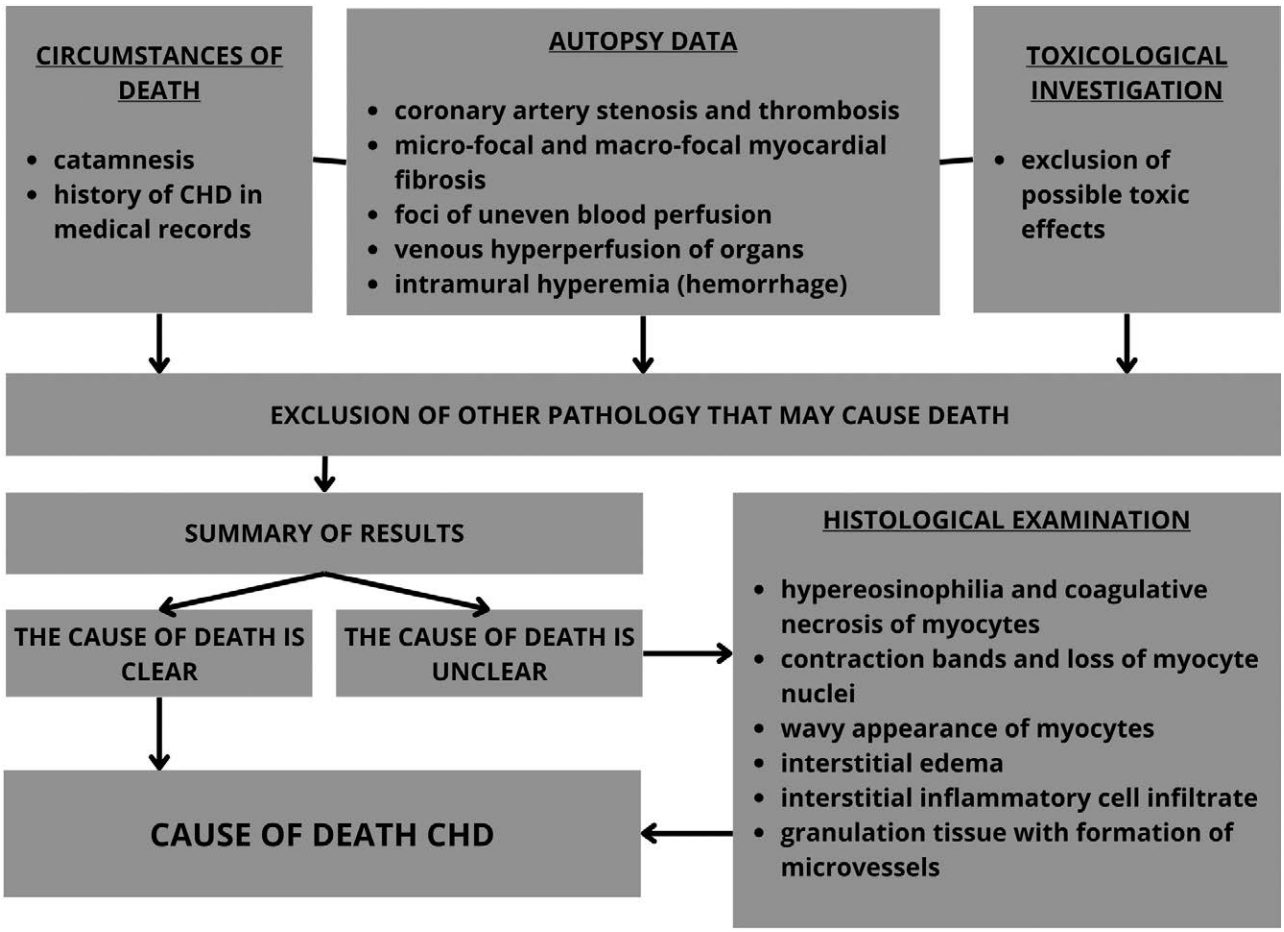

Figure 1. Forensic identification of death due to CHD principles. CHD = Coronary Heart Disease.

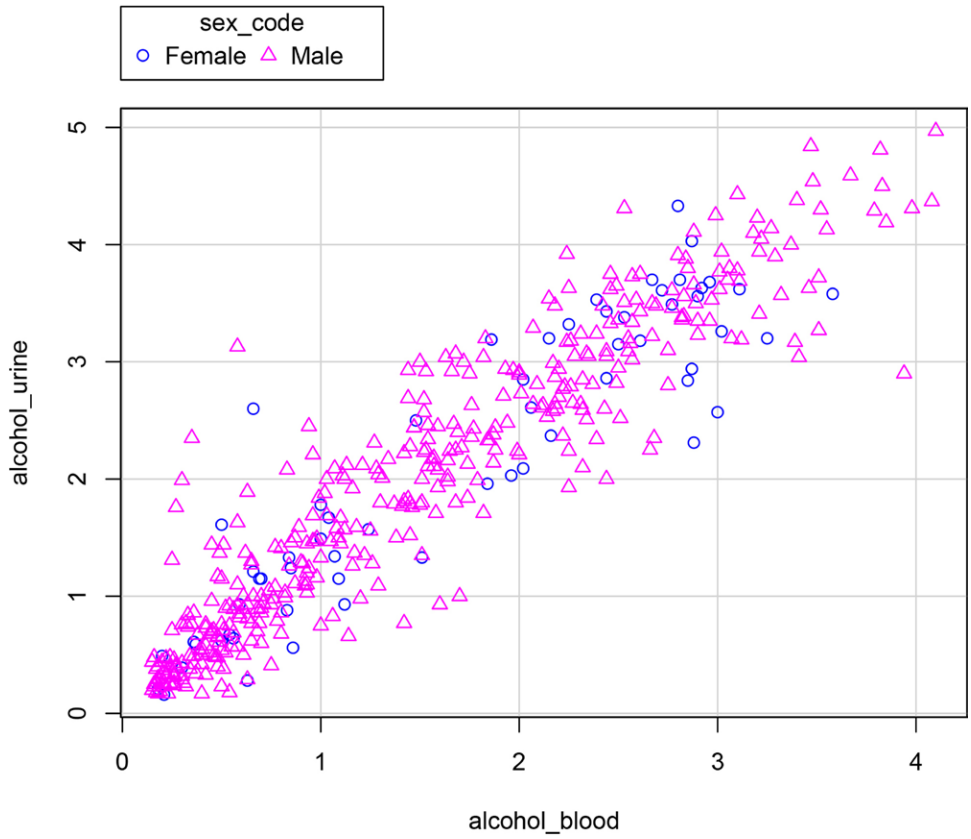

Figure 2. Correlation between alcohol in blood and in urine.

is higher, can be a much more informative indicator than blood alcohol levels alone. Assessing alcohol concentrations in both blood and urine rather than blood alone, the number of sudden deaths when ethyl alcohol was detected, has increased to 33% (n = 706). Naturally, a strong statistically significant correlation was observed between blood and urine alcohol levels $R = 0.93$ ($P < .05$) (Fig. 2).

The mean blood alcohol concentration in the whole sample was 1.37 ‰ ± 1.01, and in urine 1.73 ‰ ± 1.29. There were no significant differences between the detection frequency of the alcohol in the blood and urine ($P = .24$) (Table 1).

Concentrations greater than 1.5‰ were found in 42% (n = 260) of those who died of CHD and had alcohol in their blood, and more than 0.4‰ (which is specified in Lithuanian legislation as "drunkenness") was found in almost 80% (n = 493).

Alcohol was significantly more common in men than in women (72% and 28%, respectively, $P = .001$). (Table 2).

The mean blood alcohol concentration did not differ significantly between the male and female groups ($P = .26$). There are also no significant differences in mean urinary ethyl alcohol concentrations between the sexes ($P = .96$). Among men diagnosed with blood alcohol, 41% (n = 207) had concentrations greater than 1.5‰. Among women with a positive alcohol test, 47% (n = 91) had a blood alcohol level greater than 1.5‰.

The mean age of the whole study sample differed significantly by gender ($P < .05$) - men 60 ± 12 years; females 68 ± 14 years (Table 3).

Alcohol was more common in the younger age group of 25 to 35 years – 75%, while higher alcohol concentrations (> 1.5 ‰) were found in the 35 to 65 age group.

The potential effect of alcohol on the variability of CHD mortality depending on the day of the week and the seasons was assessed. Significantly higher blood and urine alcohol levels were observed on weekends. The highest blood alcohol concentration was on Sundays (1.51 ‰) and ranged from 0.89 ‰ (Tuesday) to 1.22 ‰ (Friday) on other days. A statistically significant difference in blood alcohol levels was observed between deaths on Friday-Sunday and Monday-Thursday ($P = .03$).

The average number of alcohol-positive sudden deaths from CHD in the winter months (December-February) was higher by about a third than in the summer-autumn months (July-August-September). The average blood alcohol level in December was almost twice as high as in August (1.43 ‰ and 0.68 ‰, respectively), and the proportion of cases where the blood or urine

Table 1

SCD distribution by alcohol concentration in blood or urine.

	Alcohol concentration, n *(%)*					
Test taken into account	**0‰**	**0.1–0.4‰**	**0.41–1.5‰**	**1.51–2.5‰**	**> 2.51‰**	**Total**
Blood	1514 (71)	137 (6)	233 (11)	151 (7)	109 (5)	2133 (100)
Urine	1601 (75)	121 (5)	154 (7)	101 (5)	165 (8)	2133 (100)

SCD = Sudden Cardiac Death.

Table 2

SCD distribution by alcohol concentration in blood by sex.

	Alcohol concentration in blood, n (%)					
	0‰	**0.1–0.4‰**	**0.41–1.5‰**	**1.51–2.5‰**	**> 2.51‰**	**Total**
Male	1090 (68)	114 (7)	190 (12)	125 (8)	82 (5)	1601 (100)
Female	337 (63)	42 (8)	62 (12)	43 (8)	48 (9)	532 (100)

SCD = Sudden Cardiac Death.

Table 3

SCD distribution by alcohol concentration in blood by age groups.

Age groups	Alcohol concentration in blood, n (%)					
	0‰	0.1–0.4‰	0.41–1.5‰	1.51–2.5‰	> 2.51‰	Total
25–35	25 (52)	2 (4)	10 (21)	8 (17)	3 (6)	48 (100)
36–45	87 (62)	6 (5)	21 (15)	17 (12)	9 (6)	140 (100)
46–55	275 (63)	33 (8)	69 (16)	32 (7)	28 (6)	437 (100)
56–65	455 (69)	49 (7)	70 (11)	48 (7)	37 (6)	659 (100)
>66	654 (79)	45 (5)	61 (7)	44 (5)	29 (4)	833 (100)

SCD = Sudden Cardiac Death.

alcohol level was higher than 0.4 ‰ was 49.7 % and 32 %, respectively (Fig. 3).

The distribution of sudden deaths according to the phases of alcohol metabolism was assessed when alcohol was found in both blood and urine (n = 451). In 88% (n = 398) of all cases of alcohol and blood alcohol, death occurred in the elimination phase (Table 4).

For the whole sample, in cases where the concentration of ethyl alcohol in the blood was lower than in the urine, the mean difference in the concentration at the elimination stage was 0.56 ± 0.41 ‰. For the whole sample, when the concentration of ethyl alcohol in the blood is higher than in the urine, the average difference in concentration during the resorption stage is 0.22 ± 0.22 ‰. The mean difference in concentration during the resorption and elimination stages was significantly different ($P < .05$).

The distribution of CHD cases depending on the level of coronary stenosis between pre-death drinkers (n = 706 [33%]) and nondrinkers (n = 1416 [67%]) was assessed. There were no statistically significant differences in stenosis between pre-death alcohol users and nondrinkers ($P = .12$) (Table 5).

However, an analysis of the group of sudden deaths from CHD in which coronary artery stenosis was relatively hemodynamically insignificant (up to 50%, n = 494) revealed that in as many as 59.9% (n = 296) of deaths alcohol was found in the blood and/ or urine. There were no statistically significant differences in mean alcohol concentrations in the study group ($P = .12$).

In the group of hemodynamically insignificant stenosis (up to 50%), death occurred statistically significantly more often in persons who consumed alcohol (in the elimination phase, 71%, $P = .001$) than in sober persons. The control group, in which acute myocardial infarction was identified as the direct cause of death with present coronary heart disease, consisted of 88 cases. Males accounted for 68.2% (n = 60) of the study group and females for 31.8% (n = 28). Age averages differed significantly by gender ($P < .05$) - males 61 ± 11 years; females 66 ± 15 years, respectively. Alcohol in the blood or urine was found in 11 subjects. The average concentration of alcohol in the blood was 1.32 ‰ ± 1.15, in urine 1.54 ‰ ± 1.36. There were no significant differences in blood and urine alcohol detection rates ($P = .13$). In all cases, death occurred in the elimination (soberizing) stage. In the group of hemodynamically insignificant stenosis (when coronary artery stenosis was less than 50%), death occurred three times more often in subjects who consumed alcohol before death than in sober subjects (73%, $P < .05$).

Table 4

CHD distribution according to the phase of alcohol metabolism.

	Resorption (when alcohol concentration in blood > alcohol concentration in urine)	*Elimination (when alcohol concentration in blood < alcohol concentration in urine)*	
0.00–0.40‰	9 (13%)	58 (87%)	n = 67 (100%)
0.41–1.5‰	23 (14%)	146 (86%)	n = 169 (100%)
1.51–2.50‰	10 (8%)	112 (92%)	n = 122 (100%)
> 2.51‰	11 (12%)	82 (88%)	n = 93 (100%)

CHD = Coronary Heart Disease.

Table 5

CHD distribution depending on arterial stenosis.

	Sudden cardiac death victims with no alcohol in blood or urine	*Sudden cardiac death with alcohol in blood or urine*
Coronary stenosis (occluded/75–95%/50–70%/≤50%)	154/951/211/100 (11%/67%/15%/7%)	67/446/122/71 (10%/63%/17%/10%)

CHD = Coronary Heart Disease.

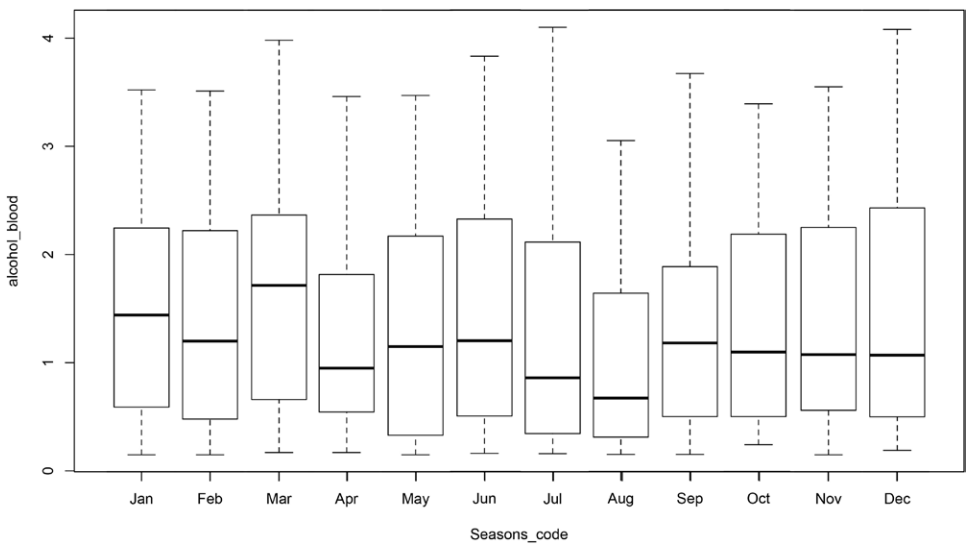

Figure 3. Mean and standard deviation of blood alcohol concentration in different months.

4. Discussion

The study has some limitations described below. First of all, the cases and parameters obtained from the Lithuanian population may not represent the situation of the global population. Furthermore, a limited number of control group cases were included in the study. Lastly, the presence of alcohol only in the blood or only in urine does not necessarily reflect the highest levels of concentration reached since the last episode of alcohol usage before death, as alcohol is often already partially metabolized and eliminated from the body.

Taking into account the results of this study, one in three people who died suddenly from CHD consumed alcohol before death. In case of a fatal outcome, alcohol was more likely to be detected in young males than in females. In the group of hemodynamically insignificant stenosis (up to 50% of the arterial lumen), death occurred statistically significantly more often in persons who consumed alcohol (in the elimination phase) than in sober persons. Since the data of the existing control and case groups are similar and without statistically significant differences, it is likely that the case group is representative in describing the sample of those who died from CHD.

The results suggest that alcohol consumption plays an important role in the seasonality of CHD mortality. A higher number of alcohol-positive sudden deaths from CHD in the winter months may be associated with holidays during the Christmas period, when alcohol consumption increases. The decrease in alcohol-related deaths from CHD in the summer-autumn months could be explained by people returning from vacation and preparing for return to work when alcohol consumption decreases. The same reason may apply for an increase in the number of alcohol-positive sudden deaths from CHD on weekends, when people are more likely to drink alcohol during their leisure time.

It is known that lower levels of coronary occlusion are found in regular drinkers compared to nondrinkers or occasional drinkers.[6] The absence of statistically significant differences in stenosis levels between pre-death drinkers and nondrinkers suggests that majority of the subjects in this study did not drink regularly.

Acute and chronic alcohol consumption can have both negative and positive effects on the cardiovascular system. In the presence of acute consumption, alcohol may impair cardiac function and cause changes in regional blood circulation, and in some cases, long-term alcohol consumption may lead to dilated cardiomyopathy.[11] On the other hand, it is thought that some mechanisms may be attributed to the protective effects of light-to-moderate alcohol consumption in CHD. These mechanisms include an increase in blood HDL-cholesterol, prostacyclin, endogenous tissue plasminogen activator, and preconditioning of the heart muscle, as well a decrease in blood LDL-cholesterol and LDL-cholesterol oxidation, blood fibrinogen, platelet adhesion, thromboxane A, decreased risk of diabetes, psychosocial stress, and improvement in endothelial function.[9,12] However, the protective effect of alcoholic beverages disappears in heavy drinkers, in part because the harmful increase in arterial blood pressure outweighs the beneficial effects of elevated HDL-cholesterol.[13] In addition, the reliability of studies showing that alcohol consumption in light-to-moderate users is associated with a reduction in the risk of CHD has been brought into question. Many of these studies have combined former drinkers and long-time abstainers. This is a confusing factor, as former drinkers have a higher mortality from CHD rate than long-time abstainers.[14] Heavy drinking is associated with an increased risk of sudden death, apparently due to an increased incidence of arrhythmias.[10]

This study suggests that alcohol consumption prior to sudden cardiac death may be detected more frequently than expected. Our observations lead to a hypothesis that in cardiac pathology, acute alcohol consumption may lead to conditions that cause electrical instability and increase the risk of sudden cardiac death. Acute alcohol consumption can cause subclinical myocardial damage and partial loss in conductivity, and hyperadrenegy, caused by toxic effects of alcohol and acetaldehyde, electrolyte imbalance, repolarization disorder, sleep apnea, and ischemia, can provoke arrhythmias.[15,16]

This study suggests that death in alcohol-positive individuals occurred most frequently during the alcohol elimination phase with hemodynamically insignificant coronary artery stenosis and relatively low alcohol concentrations. This suggests that the arrhythmogenic effects of alcohol metabolization play a key role in the thanatogenesis of sudden cardiac death in CHD.[17] The most common proarrhythmic effect of alcohol is atrial fibrillation.[18] Implied association between atrial fibrillation, oxidative stress caused by ethanol and its metabolites, and dysregulation of calcium metabolism. Studies during which it was attempted to reduce the damage to the cardiovascular system with antioxidants have not shown a positive effect of these drugs. This confirms that the association between alcohol, oxidative stress, and myocardial dysfunction is more complex.[18]

The arrhythmogenicity of alcohol is determined through several mechanisms. They are divided into direct (alcohol myotoxicity) and indirect (via alcohol metabolites or adrenal effects).[19] The following changes are observed in the body: increased adrenaline and noradrenaline secretion and heightened sympathetic tone, increased concentration of free fatty acids in plasma, decreased current of sodium ions due to direct alcohol exposure, and altered intracellular pH (acidosis at low doses of alcohol consumed, and alkalosis at high doses) via acetaldehyde.[20]

Acetaldehyde causes arrhythmias by increasing the levels of catecholamines systemically and in the heart muscle. An experimental study using dog Purkinje fibers confirmed that acetaldehyde has a proarrhythmic effect due to an increase in adrenergic tone.[19] In another study, injection of acetaldehyde directly into the dog's sinus node caused tachycardia, which was suppressed by β-adrenergic blockade. Similarly, intravenous infusion of acetaldehyde in rats caused tachycardia, the duration of which reflected the concentration of acetaldehyde in the blood. These effects have been associated with catecholamine release, as acetaldehyde increases the release of catecholamines from the bovine adrenal gland and noradrenaline from the rat brain. Acetaldehyde has also been proved to cause degranulation of presynaptic vesicles and the release of noradrenaline from the sympathetic nerve fiber limbs of the heart.[21]

Alcohol may increase the release of catecholamines from the adrenal gland or locally from the myocardium. This systemic and local increase in catecholamines may prolong the duration of the *P* wave, leading to atrial arrhythmias. However, the study did not find a significant increase in catecholamine levels between individuals who had experienced episodes of atrial fibrillation after ingestion of large amounts of alcohol in a short amount of time, and those who did not. However, the level of catecholamines in the atrial fibrillation group was higher, which does not negate that this mechanism contributes to the arrhythmic effect of alcohol. The same authors found higher levels of beta-adrenergic receptors and predominance of sympathetic neural activation of the heart in patients with a history of alcohol-related atrial fibrillation (compared with those for whom ingestion of large amounts of alcohol in a short amount of time did not induce atrial fibrillation).[19,20]

Alcohol consumption increases the concentration of free fatty acids in the plasma, which also has an arrhythmogenic effect. The mechanism is not fully understood, but a significant association between elevated free fatty acid concentrations and atrial fibrillation has been observed in the elderly.[19,20]

The reason why alcohol causes atrial fibrillation is explained by its interaction with the most important mechanisms of the heart in the onset of cardiac arrhythmias, namely atrial fibrillation. A study of "holiday heart syndrome"–cardiac activity issues due to high levels of alcohol consumption in a short

amount of time, often on holidays or weekends - found a prolongation of the PRc, QRS and QTc intervals, clearly associated with atrial fibrillation. Another study demonstrated an increase in the duration of the *P*-wave and QRS interval in 13 people soon after alcohol consumption, suggesting that alcohol impairs the propagation of electrical impulses in the atria and ventricles. Although the values mentioned in the control group also lengthened, the changes were much more pronounced in the group of alcohol users.[19,20]

In a study using stain adhesion technology (allowing ion currents to be measured in isolated cardiomyocytes up to the level of individual channels), ≥ 2 g/ l alcohol concentration inhibits cardiac sodium channels – a potential reason why acute alcohol consumption alters myocardial conduction.[22] Conductivity is altered not only by direct action on sodium channels, but also indirectly as inhibition of sodium channels may increase the activity of the sodium to calcium transducer via prolongation of action potential and repolarization, prolongation of the QT interval and facilitated onset of proximity to the heart. Inhibition of sodium channels is negligible at < 2 g/ l alcohol concentration.[19]

5. Conclusion

This study showed that pre-death alcohol consumption with CHD is a fairly common phenomenon in Lithuania. Caution should be exercised when prescribing adrenomimetics to intoxicated patients with CHD with haemodynamically insignificant coronary stenosis as CHD deaths were more common in this group, possibly in relation to alcohol-induced fatal arrhythmias. Further studies are needed to confirm these results in other populations and to assess the causal relationship between pre-death alcohol consumption and sudden cardiac death.

Author contributions

Data curation: Jurgita Stasiuniene.
Investigation: Sigitas Chmieliauskas, Sigitas Laima.
Supervision: Algimantas Jasulaitis, Pranas Serpytis.
Writing - original draft: Dmitrij Fomin.

References

[1] Health Information Centre of Institute of Hygiene, 2021. Causes of Death 2020. Available at: https://hi.lt/uploads/pdf/leidiniai/Statistikos/Mirties_priezastys/Mirties_priezastys_2020.pdf. [access date November 11, 2021].

[2] Eurostat, 2020. Deaths Due to Coronary Heart Diseases in the EU. Available at: https://ec.europa.eu/eurostat/en/web/products-eurostat-news/-/edn-20200928-1. [access date November 11, 2021].

[3] Stalioraityte E, Pangonyte D, Neimantas R. Reliability of data of death causes: comparison of premortem and verified by autopsy postmortem diagnoses. Medicina. 2004;40:690–5.

[4] Zaridze D, Maximovitch D, Lazarev A et al. Alcohol poisoning is a main determinant of recent mortality trends in Russia: evidence from a detailed analysis of mortality statistics and autopsies. Int J Epidemiol. 2009;38:143–53.

[5] O'Keefe JH, Carter MD, Lavie CJ. Primary and secondary prevention of cardiovascular diseases: a practical evidence-based approach. Mayo Clin Proc. 2009;84:741–57.

[6] Gruchow HW, Hoffmann RG, Anderson AJ, et al. Effects of drinking patterns on the relationship between alcohol an coronary occlusion. Atherosclerosis. 1982;43:393–404.

[7] Klatsky AL, Chartier D, Udaltsova N, et al. Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol. 2005;96:346–51.

[8] Regan TJ. Alcohol and the cardiovascular system. JAMA. 1990;264:377–81.

[9] Klatsky AL. Alcohol and cardiovascular diseases. Expert Rev Cardiovasc Ther. 2009;7:499–506.

[10] Panos RJ, Sutton FJ, Young-Hyman P, et al. Sudden death associated with alcohol consumption. Pacing Clin Electrophysiol. 1988;11:423–4.

[11] Friedman HS. Cardiovascular effects of alcohol with particular reference to the heart. Alcohol. 1984;1:333–9.

[12] Suzuki K, Elkind MS, Boden-Albala B, et al. Moderate alcohol consumption is associated with better endothelial function: a cross sectional study. BMC Cardiovasc Disord. 2009;9:8.

[13] Foerster M, Marques-Vidal P, Gmel G, et al. Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption. Am J Cardiol. 2009;103:361–8.

[14] Roerecke M, Rehm J. Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. Am J Epidemiol. 2011;173:245–58.

[15] Kupari M, Koskinen P. Alcohol, cardiac arrhythmias and sudden death. Novartis Found Symp. 1998;216:68–79.

[16] Rossinen J, Sinisalo J, Partanen J, et al. Effects of acute alcohol infusion on duration and dispersion of QT interval in male patients with coronary artery disease and in healthy controls. Clin Cardiol. 1999;22:591–4.

[17] Matsumoto C, Miedema MD, Ofman P, et al. An expanding knowledge of the mechanisms and effects of alcohol consuption on cardiovascular disease. J Cardiopulm Rehabil Prev. 2014;34:159–71.

[18] Laurent D, Edwards JG. Alcoholic cardiomiopathy: multigenic changes underlie cardiovascular dysfunction. J Cardiol Clin Res. 2014;2:1022.

[19] Tonelo D, Providência R, Gonçalves L. Holiday heart syndrome revisited after 34 years. Arg Bras Cardiol. 2013;101:183–9.

[20] Budzikowski AS, Daubert JP, Smith RH, et al. Holiday Heart Syndrome. Available at: http://emedicine.medscape.com/article/155050-overview. [access date November 11, 2021].

[21] Robador PA, Seyedi N, Chan NY, et al. Aldehyde dehydrogenase type 2 activation by adenosine and histamine inhibits ischemic norepinephrine release in cardiac sympathetic neurons: mediation by protein kinase Cε. J Pharmacol Exp Ther. 2012;343:97–105.

[22] Bebarova M. Advances in patch clamp technique: towards higher quality and quantity. Gen Physiol Biophys. 2012;31:131–40.