Alcohol and caffeine synergistically induce spontaneous ventricular tachyarrhythmias: ameliorated with dantrolene treatment

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BACKGROUND Alcohol and caffeine are the 2 frequently consumed substances in the general population, and the 2 substances are frequently co-consumed. Both substances may increase cardiac arrhythmia risk. However, it is unknown whether alcohol and caffeine co-consumption can synergistically enhance cardiac arrhythmogenesis.

OBJECTIVE The study sought to investigate whether caffeine and binge drinking synergistically affect cardiac arrhythmogenesis.

METHODS A binge drinking rat model (alcohol 2 g/kg, intraperitoneal, every other day for 3 times) was used. Rats (4 months old, both sexes) were randomized into the following 4 groups: binge alcohol–only group (A) (n = 8), nonalcohol, caffeine-only (60 mg/kg, intraperitoneal) group (C) (n = 8), binge alcohol plus caffeine group (A+C) (n = 8), and binge alcohol + caffeine + dantrolene group (A+D) (n = 7, treated with dantrolene 10 mg/kg before each alcohol injection). We also investigated whether alcohol induces Ca^{2+} sparks and dantrolene treatment attenuates alcohol-induced Ca^{2+} leak in ventricular myocytes.

RESULTS No arrhythmia was induced with caffeine alone (group C, n = 0 of 8) or alcohol alone (group A, n = 0 of 8). However, alcohol + caffeine induced spontaneous ventricular tachyarrhythmias in all rats (group A+C, n = 8 of 8; $P < .001$ vs group C or A). Dantrolene prevented ventricular tachyarrhythmia induction in all 7 rats (group A+D, n = 0 of 7; $P < .001$ vs group A+C). In isolated ventricular myocytes, alcohol significantly increased Ca^{2+} sparks and dantrolene treatment reduced alcohol-induced Ca^{2+} sparks.

CONCLUSION Co-consumption of caffeine and binge drinking synergistically promote spontaneous ventricular tachyarrhythmias in rats. Dantrolene treatment can decrease alcohol-enhanced Ca^{2+} sparks in vitro and prevented alcohol and caffeine induced ventricular tachyarrhythmias in vivo.

KEYWORDS Alcohol; Caffeine; Arrhythmogenesis; Ventricular tachyarrhythmia; Bidirectional ventricular tachycardia; Dantrolene

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Introduction

Alcohol (in beers, wines, etc.) and caffeine (commonly in coffee) are the 2 most widely consumed substances worldwide. According to the 2019 National Survey on Drug Use and Health, 85.6% of people 18 years of age and older reported that they drank alcohol at some point in their lifetime, while 25.8% of people reported that they engaged in binge drinking in the past month.[1] Alcohol consumption, especially binge drinking, is a recognized risk factor for cardiac arrhythmias. Alcohol-induced arrhythmias are commonly known as the holiday heart syndrome.[2] Among holiday heart syndrome patients, atrial fibrillation (AF) is the most frequently diagnosed arrhythmia.[2]

Caffeine is also frequently consumed in the general population. There is an estimate that more than 85% of adults in the United States regularly consume coffee. Caffeine is generally considered as a potential trigger for cardiac arrhythmias in clinical practice by physicians,[3] as well as reported by patients.[4] However, the current clinical evidence is conflicting regarding caffeine consumption and cardiac arrhythmias. There are epidemiological data suggesting that caffeine consumption is not associated with cardiac arrhythmias; conversely, it may even be beneficial in reducing the arrhythmia risk.[5–7] Nevertheless, there are case reports with documented cardiac arrhythmias and sudden death due to high dose of caffeine intake.[8]

Alcohol and caffeine are frequently co-consumed and the co-consumption of alcohol and caffeine is becoming a public

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KEY FINDINGS

- We have demonstrated in rats that alcohol and caffeine, 2 widely consumed substances, can synergistically induce ventricular tachyarrhythmias, especially bidirectional ventricular tachycardia.
- Our results indicate that co-consumption of alcohol and caffeine could enhance ventricular tachyarrhythmias and potentially sudden cardiac death in the general population.
- Dantrolene treatment can decrease alcohol induced calcium sparks in ventricular myocytes and prevent alcohol and caffeine–enhanced ventricular tachyarrhythmias in vivo.
- Stabilizing cardiac ryanodine receptor with dantrolene treatment could prevent alcohol and caffeine–enhanced ventricular tachyarrhythmias.

health concern.[9,10] There is a significant link between alcohol and caffeine intake, with alcoholic individuals consuming more caffeine compared with nonalcoholic individuals.[9] Despite the fact that both alcohol and caffeine have the potential to trigger cardiac arrhythmias and they are frequently co-consumed, the interaction of alcohol and caffeine on cardiac arrhythmogenesis has not been studied. We hypothesized here that alcohol and caffeine can synergistically enhance cardiac arrhythmogenesis. Accordingly, the current study was designed to test this hypothesis.

Because studies from us[11] as well as from others[12] have shown that binge alcohol enhanced AF is mediated by cardiac ryanodine receptor (RyR2) dysfunction and Ca^{2+} leak, and stabilizing RyR2 with dantrolene treatment can decrease AF inducibility in binge drinking animals.[11] Here, we have also tested whether stabilizing RyR2 with dantrolene treatment can decrease alcohol and caffeine-induced cardiac arrhythmogenesis.

Methods

Binge alcohol rat model and experimental design

Adult (4-month-old) Sprague Dawley rats of both sexes were used in this study. A binge drinking rat model was established with alcohol injection (2 g/kg, diluted in saline, intraperitoneal) 3 times, every other day (ie, on days 1, 3, and 5), as described in our previous reports with minor modifications (given 3 times instead of 4 times).[11] To test whether alcohol and caffeine synergistically induce cardiac arrhythmogenesis in this model, a single dose of caffeine (60 mg/kg, intraperitoneal; Sigma-Aldrich, St. Louis, MO) was given 3 hours after the last alcohol injection. This study consisted of the following 4 groups (Table 1): (1) in the nonalcohol, caffeine-only group (group C) (n = 8), rats received 3 injections of saline instead of alcohol and a single dose of caffeine 3 hours after the last saline injection; (2) in the binge alcohol group (group A) (n = 8), rats received 3 alcohol injections but no caffeine (only saline) injection; (3) in the binge alcohol plus caffeine group (group A+C) (n = 8), rats received 3 alcohol injections plus a single dose of caffeine injection 3 hours after the last alcohol injection; and (4) in the binge alcohol plus caffeine treated with dantrolene (group A+D) (n = 7), rats received dantrolene (10 mg/kg, intraperitoneal; Sigma-Aldrich) before receiving alcohol (2 g/kg, intraperitoneal) injections (3 times, once every other day) plus a single dose of caffeine injection 3 hours after the last alcohol injection. Note that a single dose of caffeine (60 mg/kg, intraperitoneal) was administered 3 hours after the last alcohol or saline injection on day 5 in group C, group A+C, and group A+D, while the equivalent saline was given in group A.

Table 1 Study groups

Group	A	C	D
C	–	+	–
A	+	–	–
A+C	+	+	–
A+D	+	+	+

+: with (or administered); –: without.
A = alcohol; C = caffeine; D = dantrolene.

Rats were housed in our institutional animal care facility and kept on a 12-hour light–dark cycle with food and water available ad libitum. The use of animals was approved by the Institutional Animal Care and Use Committee at the New York Institute of Technology College of Osteopathic Medicine and was in accordance with the Guide for the Care and Use of Laboratory Animals.

Echocardiography

To evaluate the effects of binge drinking on cardiac function, echocardiography was taken 3 hours after the last alcohol or saline injection just prior to the caffeine administration. Rats were subjected to echocardiographic measurements using a VisualSonics Vevo 3100 platform (FujiFilm VisualSonics, Toronto, Ontario, Canada) coupled with an ultrasound transducer probe (25 MHz), as we have reported previously.[11] Rats were anesthetized with isoflurane (1.5%), and 2-dimensional echocardiograms were obtained from short axis (at the papillary muscle level) and long axis of the left ventricle (LV). We used 2-dimensionally targeted M-mode echocardiograms to determine LV wall thickness and chamber dimensions in systole and diastole from short-axis view. The following parameters were measured: LV anterior wall thickness in end-diastole and end-systole, LV diastolic and systolic internal diameters, LV posterior wall thickness in end-diastole and end-systole, and LV fractional shortening.

Electrocardiography monitoring and arrhythmia induction

Standard electrocardiography lead II was recorded continuously 5 minutes before the arrhythmia induction with caffeine injection (60 mg/kg, intraperitoneal) in all groups except group A, in which saline instead of caffeine was

administrated. The electrocardiography recording lasted 30 minutes after caffeine–saline injection, or until arrhythmias terminated in case arrhythmias lasted more than 30 minutes.

Blood alcohol level

Blood samples were taken from 8 nonalcohol control rats and 8 rats treated with alcohol 3 hours after the last injection (saline or alcohol in respective groups) before caffeine injection. Blood alcohol levels were measured using an Ethanol Assay Kit (Abcam, Cambridge, United Kingdom; catalog number ab272531; detection range 0.04%–2% alcohol), according to the manufacturer's recommended protocol.

Blood norepinephrine level

To investigate whether alcohol activates the sympathetic nervous system, blood norepinephrine levels were determined in 6 nonalcohol control rats and 6 alcohol treated rats using an enzyme-linked immunosorbent assay kit (Noradrenaline/Norepinephrine ELISA kit; MyBioSource, San Diego, CA; catalog number MBS760375; detection range 15.625–1000 pg/mL), according to the manufacturer's recommended protocol, as previously reported.[11]

Calcium spark (leak) measurement in isolated ventricular myocytes

To investigate whether alcohol causes calcium (Ca^{2+}) leak and whether dantrolene treatment can decrease alcohol enhanced Ca^{2+} leak in ventricular myocytes, we measured Ca^{2+} sparks in isolated ventricular myocytes. Ventricular myocytes were isolated from 6 normal rats using an established enzymatic digestion protocol, as previously reported.[13] The isolated myocytes from each rat were randomized into control, alcohol, and alcohol plus dantrolene groups and plated onto 35 mm laminin-coated glass-bottom dishes. Myocytes in alcohol group were treated with alcohol (50 mM) in culture media for 24 hours, while myocytes in the alcohol plus dantrolene group were treated with alcohol (50 mM) + dantrolene (10 μM) in culture media for 24 hours. The alcohol and dantrolene concentrations have been used previously in atrial myocytes.[11,12]

After 24-hour treatment, myocytes were loaded with Fluo-4 AM (5 μM; Invitrogen, Waltham, MA) in normal Tyrode solution for 20 minutes at room temperature. After brief washing, spontaneous Ca^{2+} sparks were obtained in quiescent cells after 1 Hz stimulation (for 1 minute) to promote equal sarcoplasmic reticulum Ca^{2+} load, as previously reported.[11] Ca^{2+} sparks were recorded using a Zeiss LSM 980 Airyscan2 Inverted Confocal Laser Scanning Super-resolution Microscope with a ×40, 1.2 NA objective and the ZEN 3.0 imaging software (Carl Zeiss Microscopy, White Plains, NY). Fluo-4 was excited at 488 nm and fluorescence emission was measured at 517 nm. Images were acquired in the line-scan mode (X-T) with a rate of 300 lines per second and pixel dimension of 0.099 × 0.099 μm, for a total of 1800 frames. Ca^{2+} spark images were recorded from 10 randomly selected myocytes for each animal. Obtained images were analyzed with the SparkMaster plugin and the ImageJ software (version 1.53e, National Institutes of Health, Bethesda, MD). For each rat, Ca^{2+} spark data were measured and averaged from 10 randomly selected myocytes.

Table 2 Echocardiographic parameters in control and alcohol groups

	Control (n = 6)	Alcohol (n = 6)
HR, beats/min	342 ± 17	319 ± 28
LVAWTd, mm	1.66 ± 0.19	1.52 ± 0.17
LVAWTs, mm	2.70 ± 0.44	2.62 ± 0.31
LVDd, mm	6.54 ± 0.74	5.86 ± 0.38
LVDs, mm	3.32 ± 0.71	2.54 ± 0.47
LVPWTd, mm	1.57 ± 0.21	1.56 ± 0.14
LVPWTs, mm	2.70 ± 0.29	2.65 ± 0.27
LVFS, %	50.5 ± 7.9	51.6 ± 3.0

Values are mean ± SD. Alcohol group: rats received alcohol injections (2 g/kg, intraperitoneal) 3 times every other day; control group: rats received saline injection 3 times every other day. These rats did not receive caffeine when the echocardiography was being taken in both groups. $P > .05$ for all parameters.

HR = heart rate; LVAWTd = left ventricular anterior wall thickness in diastole; LVAWTs = left ventricular anterior wall thickness in systole; LVDd = left ventricular diameter in diastole; LVDs = left ventricular diameter in systole; LVFS = left ventricular fractional shortening; LVPWTd = left ventricular posterior wall thickness in diastole; LVPWTs = left ventricular posterior wall thickness in systole.

Statistical analysis

Data are expressed as mean ± SD where appropriate. Normally distributed data such as echocardiographic data, blood alcohol, and norepinephrine levels between 2 groups (control and alcohol groups) were compared using the Student *t* test. Data collected from more than 2 groups (eg, Ca^{2+} sparks) were first analyzed using the 1-way analysis of variance followed by the post hoc analysis. Fisher's exact test was used to compare the arrythmia incidence. All data analyses was performed using GraphPad Prism 8 software (GraphPad Software, San Diego, CA). $P < .05$ was accepted as statistically significant.

Results

Blood alcohol and norepinephrine levels

Compared with the control rats receiving saline injections, the blood alcohol level was significantly increased in the alcohol rats 3 hours after the injection (0.45 ± 0.32% in alcohol group, n = 8), while it was not detectable (below the detection threshold) in control group (n = 8).

Compared with the control rats receiving saline injections, the blood norepinephrine level was significantly higher in the alcohol group 3 hours after the injection (619 ± 56 pg/mL in alcohol rats [n = 6] vs 299 ± 132 pg/mL in control rats [n = 6]; $P < .001$).

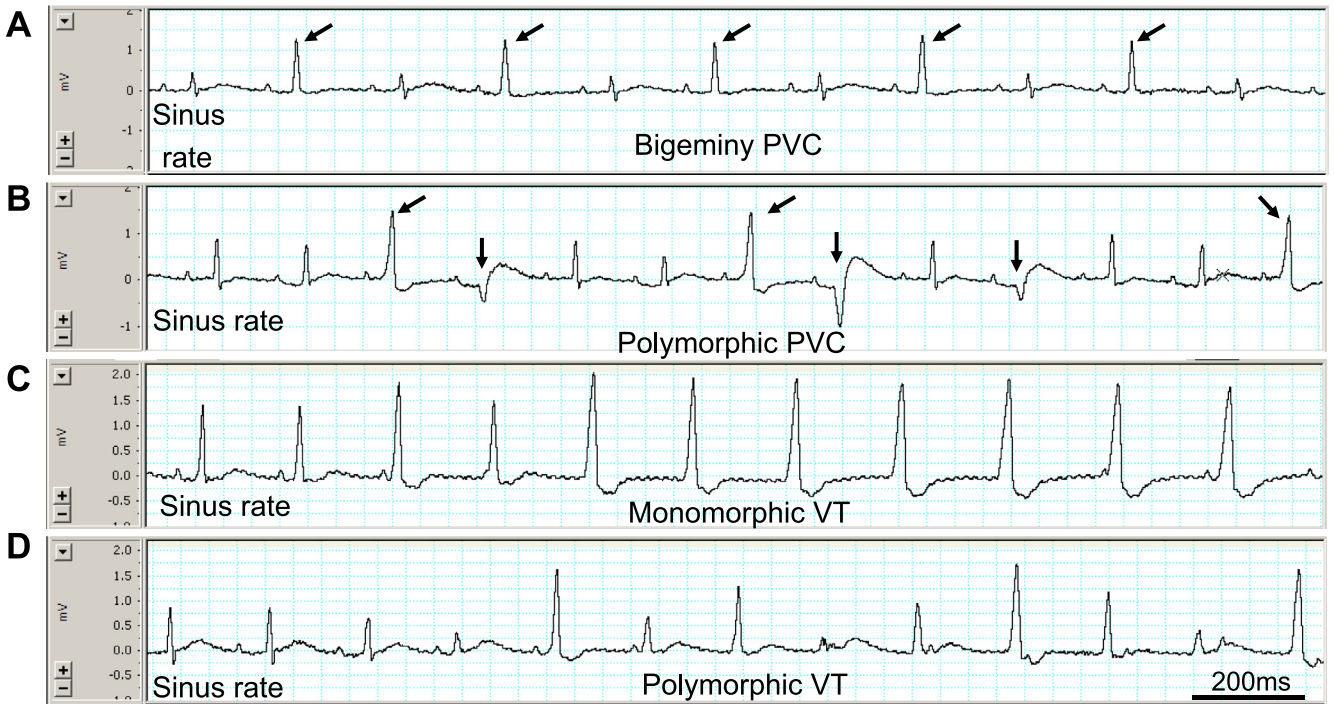

Figure 1 Electrocardiography recording of various ventricular tachyarrhythmias induced by binge alcohol and caffeine co-consumption. **A:** Bigeminy premature ventricular contractions (PVCs) (indicated by arrows); **B:** polymorphic PVCs (arrows); **C:** monomorphic ventricular tachycardia (VT); **D:** polymorphic VT.

Echocardiographic parameters

Compared with the control animals receiving saline injections, rats received alcohol injection did not show significant differences in echocardiographic parameters regarding LV wall thickness, chamber dimensions, and fractional shortening (Table 2).

Cardiac arrhythmias

No arrhythmia was induced in the nonalcohol group after caffeine administration (n = 0 of 8 in group C). No arrhythmia was observed in the binge alcohol rats (n = 0 of 8 in group A) after saline injection (without caffeine). In contrast, binge alcohol plus caffeine induced spontaneous ventricular tachyarrhythmias in all rats (n = 8 of 8 in group A+C; $P < .001$ vs the control groups). The induced ventricular tachyarrhythmias included various premature ventricular contractions (PVCs) in all rats (Figure 1), monomorphic ventricular tachycardia (VT) in 2 rats (Figure 1), polymorphic VT (Figure 1), and bidirectional VT in 7 of 8 rats (Figure 2). Note that different types of ventricular arrhythmias could be seen in the same animal from time to time. Ventricular arrhythmias (typically started with PVCs) were initiated 3.8 ± 1.7 minutes after caffeine injection and lasted for 23.6 ± 19.8 minutes (ranging from 7 minutes to more than 1 hour). No atrial arrhythmia was observed. Dantrolene treatment prevented arrhythmia induction in all 7 rats (n = 0 of 7 in group A+D; $P < .001$ vs group A+C).

Ca^{2+} sparks

Compared with control ventricular myocytes, 24-hour alcohol treatment significantly increased Ca^{2+} sparks in culture (Figure 3), and dantrolene treatment decreased Ca^{2+} sparks in myocytes treated with alcohol (Figure 3).

Discussion

Major findings

To our knowledge, this is the first study designed to investigate the synergistic effect of alcohol and caffeine on cardiac arrhythmogenesis in an animal model. For the given doses, neither alcohol nor caffeine alone induced cardiac arrhythmias, but the combination of the two induced ventricular tachyarrhythmias in all animals, indicating a synergistic effect of alcohol and caffeine in inducing ventricular tachyarrhythmias. It is interesting to note that a specific type of VT, bidirectional VT (Figure 2), was induced in a majority of rats (n = 7 of 8) in this animal model, while no atrial arrythmias were observed. Moreover, the ventricular arrhythmia inducibility could be suppressed with dantrolene treatment. We also demonstrated in vitro that alcohol treatment enhanced Ca^{2+} leak in isolated ventricular myocytes and dantrolene treatment reduced Ca^{2+} leak. Thus, stabilizing the RyR2 with dantrolene treatment could be a therapeutic strategy in this condition.

Alcohol, caffeine, and cardiac arrhythmias

The arrhythmogenic effect of alcohol has been well recognized, and AF is the most frequently diagnosed arrhythmia in patients with holiday heart syndrome.[2] The AF promotion effect by alcohol has been supported by recent experimental data showing an enhanced AF inducibility in various binge alcohol animal models.[11,12] The effect of alcohol on

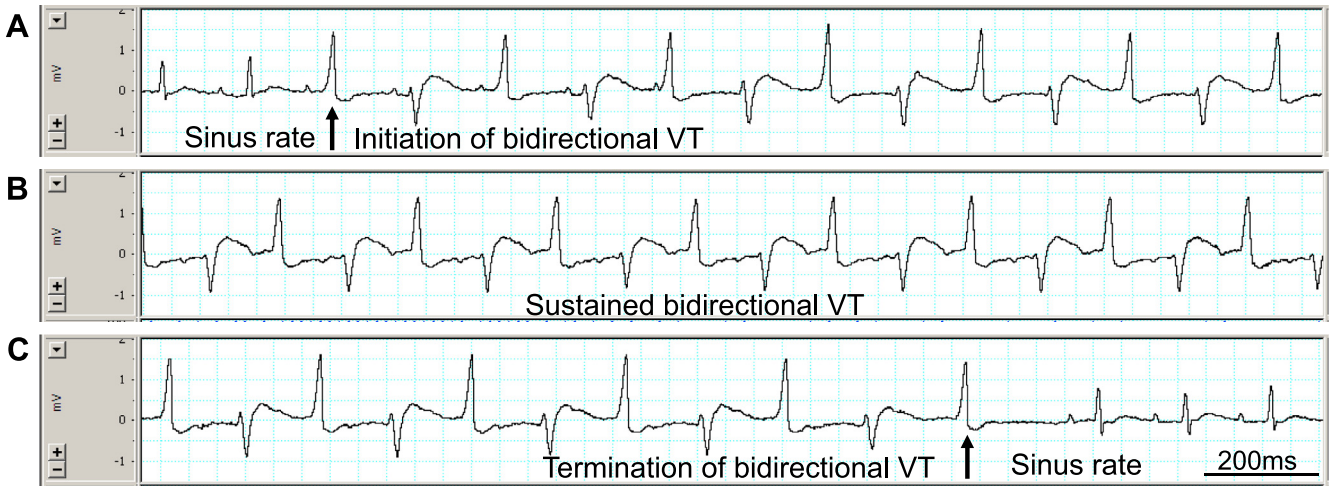

Figure 2 An example of electrocardiography recording of bidirectional ventricular tachycardia (VT). **A:** Sinus rate is seen at the beginning, followed by the initiation of bidirectional VT; **B:** sustained bidirectional VT; **C:** termination of bidirectional VT and return of sinus rate.

ventricular arrhythmogenesis is less known.[14] There were autopsy data suggesting that alcohol abusers died suddenly more often than expected.[15] Up to one-fourth of sudden cardiac deaths in young and middle-aged adults may be linked to heavy drinking with fatty liver degeneration.[15] There are also reports that alcohol consumption is associated with an increased incidence of sudden cardiac death in men.[16] Epidemiological data also showed that heavy drinking (consuming more than 6 drinks/d) is associated with an increased risk of sudden death.[17] There are experimental data showing that long-term ethanol administration (36% of daily calories for 1 year) resulted in prolonged intraventricular conduction and morphological changes in the ventricular myocardium.[18]

Caffeine is generally considered as a potential trigger for cardiac arrhythmias in clinical practice. This was also reported by patients in a recent study.[4] However, the typical daily doses of caffeine in coffee or tea are not associated with cardiac arrhythmias.[3] In fact, epidemiological data indicate that caffeine consumption is associated with a mild reduction in the incidence of AF or of any other arrhythmias.[6,7] It has been reported that chronic consumption of caffeinated products was not associated with either atrial or ventricular premature contractions.[19] A meta-analysis of 7 human studies found that caffeine consumption had no impact on incidence of ventricular arrhythmias.[20] Nevertheless, a recent observation in healthy subjects found that

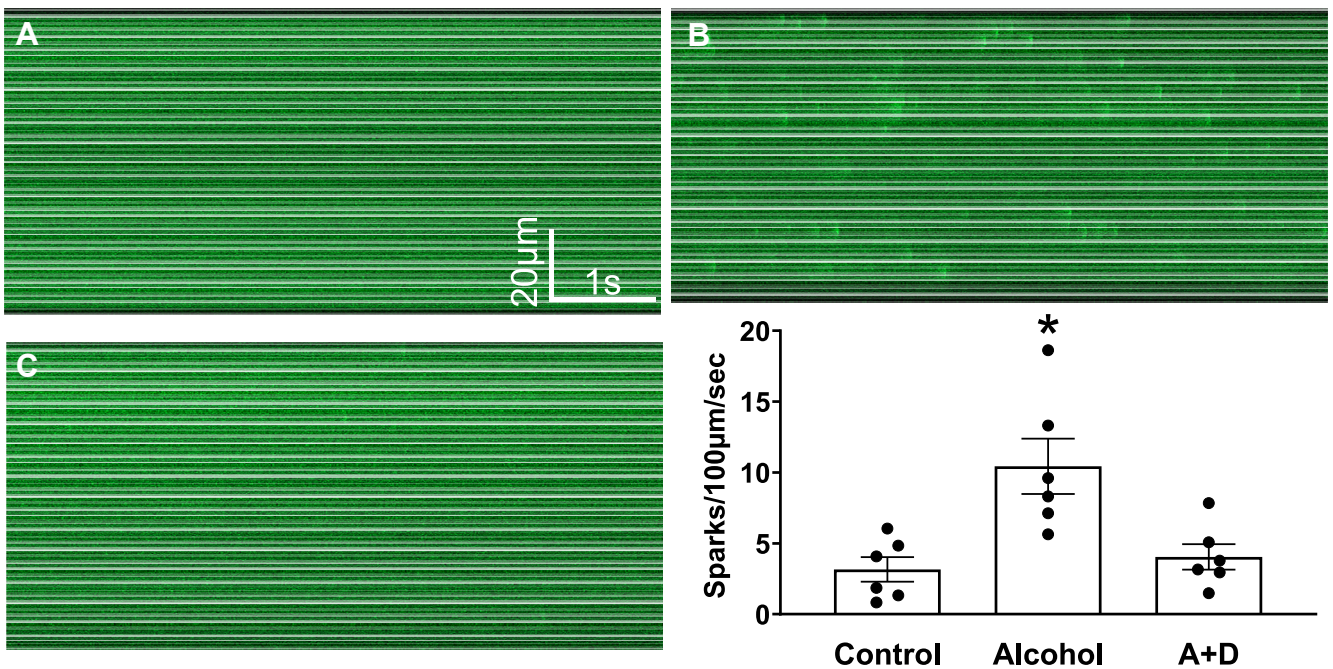

Figure 3 Calcium sparks in isolated ventricular myocytes 24 hours after different treatments. Examples of confocal line scanning images of the calcium sparks from control group **(A)**, alcohol group **(B)**, and alcohol + dantrolene (A+D) group **(C)** are shown. The bar graph shows the qualitative calcium spark data. Data are expressed as mean ± SD; n = 6 in all groups. *$P < .05$ vs the control and A+D groups.

drinking more than 1 cup per day of coffee increased PVCs.[21] Moreover, high-dose caffeine has been shown experimentally to induce ventricular tachyarrhythmias and deaths. Intravenous infusion of caffeine (15 mg/kg/min) in rats induced ventricular ectopic beats (started after 22.8 minutes) and developed fatal ventricular fibrillation in all animals by 66.9 minutes.[22] We have demonstrated recently that caffeine and dobutamine challenge can induce ventricular tachyarrhythmias and bidirectional VT in normal rats.[23]

Co-consumption of alcohol and caffeine on cardiac arrhythmias

Co-consumption of alcohol and caffeine is common and is becoming a public health concern.[9,10] Caffeine is a central nervous system stimulant and has been used as a cognitive enhancer to increase alertness and attentional performance.[24] This is probably one of the reasons people take caffeine after drinking alcohol or mixing caffeine with alcohol to try to keep awake. It is known that caffeine does not increase alcohol metabolism,[10] and it may mask the depressant effects of alcohol, making drinkers feel more alert than they would otherwise and leading to more excessive drinking.[9] Some behavioral evidence also suggests that caffeine can increase alcohol drinking and binge drinking episodes, which in turn can foster the development of alcohol dependence.[9] The deleterious effects of alcohol abuse may be exacerbated by mixing caffeine with alcohol. As such, previous studies on alcohol-caffeine co-consumption were largely focused on the adverse effects of co-consumption on increased alcohol drinking and related damages.[9] There is no specific report on cardiac arrhythmogenesis.

To our knowledge, this is the first study having examined the synergistic effect of alcohol and caffeine on promoting cardiac arrhythmogenesis and demonstrating a clear synergistic effect of alcohol and caffeine in inducing ventricular tachyarrhythmias. It should be noted that although various ventricular tachyarrhythmias were induced, a specific, characteristic bidirectional VT was prevalent in this animal model, seen in 7 of 8 rats. No atrial arrhythmias were observed. Thus, co-consumption of alcohol and caffeine seems to selectively promote spontaneous ventricular tachyarrhythmias, especially bidirectional VT. Our results suggest a potential risk of triggering ventricular tachyarrhythmias and sudden cardiac death when a large amount of alcohol and caffeine are co-consumed.

Potential mechanism for alcohol and caffeine co-consumption–induced ventricular arrhythmia

The cardiac effects of alcohol are complex and dose-dependent.[25] We used echocardiography to evaluate cardiac function 3 hours after the last alcohol injection and found that alcohol did not significantly affect cardiac function in this study. Our results are consistent with reports that binge drinking did not affect LV function postbinge in patients.[26] However, it has been reported that alcohol can depress cardiac contraction in isolated cardiac tissue.[27] This discrepancy between in vitro and in vivo effect could be explained in part by the sympathetic activation seen in vivo. We found that alcohol increased norepinephrine levels, which is consistent with other reports that alcohol increased sympathetic tone.[26] Activation of the sympathetic nervous system could theoretically alleviate alcohol's direct cardiac suppressive effects.

We as well as others have shown that alcohol can lead to RyR2 dysfunction and Ca^{2+} leak, enhancing AF arrhythmogenesis.[11,12] In this study, we have confirmed that alcohol increased Ca^{2+} leak in isolated ventricular myocytes in culture. Caffeine is a known RyR2 agonist and can decrease the sarcoplasmic reticulum store–operated Ca^{2+} threshold.[28] The reduced threshold sensitizes the RyR2 to activation by the luminal Ca^{2+}, resulting in spontaneous Ca^{2+} release, known as store overload–induced Ca^{2+} release.[28] These effects could exacerbate RyR2 dysfunction and Ca^{2+} leak, promoting arrhythmogenesis. We also confirmed that stabilizing RyR2 with dantrolene treatment could decrease alcohol-enhanced Ca^{2+} leak in isolated ventricular myocytes and prevent alcohol and caffeine induced ventricular tachyarrhythmias in vivo, suggesting that RyR2 dysfunction and Ca^{2+} leak play an important role in alcohol and caffeine–induced ventricular arrhythmogenesis.

AF is reportedly the most common arrhythmia induced by alcohol.[2,29,30] It is interesting to note that in this study we found that co-consumption of alcohol and caffeine promoted various ventricular tachyarrhythmias but not atrial arrhythmias. While the exact mechanism for this remains to be investigated, it has been reported that Purkinje fibers in ventricles display a greater propensity to develop Ca^{2+} handling abnormalities and arrhythmic triggers in animal models and humans with catecholaminergic polymorphic VT.[31] It could be speculated that similar mechanism could be responsible for the ventricular arrhythmias observed in this model. This could also explain that no atrial arrhythmias were observed.

Clinical implications and study limitations

We have demonstrated experimentally in this study that the 2 most commonly consumed substances (alcohol and caffeine) can synergistically induce ventricular tachyarrhythmias in rats. This may have important clinical implications considering the common occurrence of co-consumption of alcohol and caffeine in the general population.

However, there are limitations in directly extrapolating these results to humans. The equivalent dosages of alcohol and caffeine in humans and rats are unknown. Due to differences in basic cardiac electrophysiology and cardiac action potentials between rats and humans,[32] there may be interspecies differences in sensitivity to these substances. Thus, human data are needed to confirm these results.

While the doses of alcohol and caffeine used in these rats seemed high from a human perspective, it should be noted that rats generally tolerate much higher pharmacological doses (typically 6–7 times higher per kilogram of body weight) than human beings, due to their higher metabolic

rates.[33] Even though the exact human equivalent doses of alcohol and caffeine remain unknown, if the general scaling of one-sixth could be applied,[33] then consuming alcohol (0.33 g/kg) and caffeine (10 mg/kg) could be seen in humans.

Conclusion

We have demonstrated in this study that caffeine and binge drinking synergistically promote spontaneous ventricular tachyarrhythmias in rats, indicating that caffeine and binge drinking could lead to increased risk of developing lethal ventricular tachyarrhythmias and sudden cardiac death. Our results have also shown that by stabilizing RyR2 and reducing Ca^{2+} leak, dantrolene treatment can prevent ventricular tachyarrhythmias in this animal model.

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