ORIGINAL RESEARCH

Impact of High Volume Energy Drink Consumption on Electrocardiographic and Blood Pressure Parameters: A Randomized Trial

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***Background*—**Energy drinks have been linked to an increase in emergency room visits and deaths. We aim to determine the impact of energy drinks on electrocardiographic and hemodynamic parameters in young healthy volunteers.

***Methods and Results*—**A randomized, double-masked, placebo-controlled, crossover study was conducted in healthy volunteers. Participants consumed 32 oz of either energy drink A, energy drink B, or placebo within 60 minutes on 3 study days with a 6-day washout period in between. The primary end point of QTc interval and secondary end points of QT interval, PR interval, QRS duration, heart rate, and brachial and central blood pressures were measured at baseline, and every 30 minutes for 240 minutes. A repeated-measures 2-way analysis of variance was performed with the main effects of intervention, time, and an interaction of intervention and time. Thirty-four participants were included (age 22.1±3.0 years). The interaction term of intervention and time was statistically significant for Bazett's corrected QT interval, Fridericia's corrected QT interval, QT, PR, QRS duration, heart rate, systolic blood pressure, diastolic blood pressure, central systolic blood pressure, and central diastolic blood pressure (all $P<0.001$). The maximum change from baseline in Bazett's corrected QT interval for drinks A, B, and placebo were +17.9±13.9, +19.6±15.8, and +11.9±11.1 ms, respectively ($P=0.005$ for ANOVA) ($P=0.04$ and <0.01, respectively compared with placebo). Peripheral and central systolic and diastolic blood pressure were statistically significantly different compared with placebo (all $P<0.001$).

***Conclusion*—**Energy drinks significantly prolong the QTc interval and raise blood pressure.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT03196908. **(*J Am Heart Assoc*. 2019;8: e011318. DOI: 10.1161/JAHA.118.011318.)**

Key Words: blood pressure • electrocardiography • energy drinks • hemodynamics • QT interval electocardiography

Energy drinks are a growing industry with a market value predicted to reach $61 billion by 2021.[1] It is estimated that about 30% of teenagers between the ages of 12 through 17 years in the United States consume energy drinks on a regular basis.[2] A study of military personnel found that nearly 45% of deployed service members consumed at least 1 energy drink per day with 14% drinking ≥3 daily.[3] Although commonly promoted as supplements that can boost performance and cognition, these drinks have also been reported to have numerous detrimental side effects, particularly cardiovascular and neurological in nature.[4–6] The number of annual emergency department visits involving energy drinks increased from 10 068 in 2007 to 20 783 in 2011.[7] According to the Food and Drug Administration, there have been 34 deaths attributed to energy drinks warranting investigation into the safety of these beverages.[8]

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011318

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Clinical Perspective

What Is New?

- The class of energy drinks, rather than one particular product affect the QTc interval and blood pressure.

What Are the Clinical Implications?

- Individuals with acquired or congenital long QT syndrome and those with hypertension should be more vigilant and limit their energy drink intake.

Energy drink consumption has been associated with cardiac arrest, myocardial infarction, spontaneous coronary dissection, and coronary vasospasm.[9–16] This association is strengthened with studies showing increased platelet aggregation, increased systolic blood pressure (SBP), and QTc prolongation.[17–20] QT/QTc interval prolongation is a biologically plausible reason for the sudden cardiac arrest associated with energy drinks and QTc prolongation places patients at increased risk for developing torsades de pointes, which can lead to fatal ventricular arrhythmias.[21] Several small studies have demonstrated mild QTc prolongation with energy drink consumption but the data remain controversial because of energy drink dose and study design-related confounders.[19,20,22,23] To validate previous electrocardiographic findings and to assess the differences between energy drink types, we conducted a randomized, double-masked, placebo-controlled, crossover study in young healthy volunteers.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

This study was approved by the Institutional Review Board (IRB) at University of the Pacific (Stockton, CA). All participants were provided written informed consent consistent with university requirements for clinical studies involving human subjects. The clinical study was registered on ClinicalTrials.gov (NCT03196908).

This was a randomized, double-masked (participants and care providers), placebo-controlled, crossover clinical trial conducted at a university campus setting (July 2017 to December 2017). Healthy volunteers between the ages of 18 and 40 years who were willing to avoid ingestion of caffeine and energy drinks for 48 hours before each study day were eligible for enrollment. Participants were excluded if they had any known medical condition (confirmed through participant interview), were pregnant or breastfeeding, were current smokers, had a baseline QTc >450 ms, or brachial blood pressure >140/90 mm Hg. Those who were taking any chronic prescription or over-the-counter medications were excluded except those who had been taking oral contraceptives for over 1 month. An overnight fast (with allowance for water only) was required preceding every study day, and no food was allowed during the study monitoring period. A commercially available non-caffeinated granola bar (Nature Valley Crunchy Oats 'N Honey, General Mills) was provided after the 180-minute time point upon participant request.

Participants were randomized into 1 of 3 intervention phases using a computer-generated code from http://www.randomization.com. Participants received two 16-oz bottles of a commercially available caffeinated energy drink brand (drink A), another brand of a caffeinated energy drink (drink B), or a placebo-drink (placebo) on 3 separate days with a minimum 6-day washout period in-between. The beverages were consumed within a 60-minute period but no faster than 1 bottle in 30 minutes. Based on the package labeling, both drink A and drink B contained caffeine (304–320 mg/32-fl oz), taurine, glucuronolactone, and vitamins along with other proprietary ingredients.[24] Some differences between the 2 energy drink brands include the presence of carnitine, guarana, and panax ginseng. The placebo drink contained carbonated water, lime juice, and cherry flavoring. All drinks were packaged in identical, masked containers prepared within 24 hours of administration and stored in a refrigerator before administration.

End Point Measurement

The primary end point was QTc interval. Secondary end points included the QT interval (QT), PR interval (PR), QRS duration (QRSd), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), central systolic blood pressure (cSBP), and central diastolic blood pressure (cDBP). Augmentation index (AI) adjusted to an HR of 75 bpm was also measured and will be reported in a separate analysis. All end points were measured at baseline and at 30, 60, 90, 120, 150, 180, 210, and 240 minutes on each study day. Participants began the study at approximately the same time each study day to account for circadian rhythm changes.

A standard 12-lead ECG (PageWriter Trim III or TC20, Phillips) was obtained with participants in the supine position. ECGs were performed in triplicate at each time point ≈1 minute apart and averaged. The machine reported HR, PR interval, QRSd, QT interval, and QTc interval (Bazett's formula [QTcB]) end points were used for analysis. QTc was also corrected using Fridericia's formula (QTcF) where QTcF=QT/cube-root of (RR interval).

Blood pressure measurements were obtained in the seated position after an initial rest period of 8 minutes using an automated blood pressure device (SphygmoCor XCEL PWA, AtCor Medical). SphygmoCor provides automated brachial

blood pressure as well as non-invasive analysis of the central aortic blood pressure waveform and related hemodynamic parameters. Two measurements were taken at each time point ≈2 minutes apart on the right arm and averaged.

Statistical Analysis

Based on previous studies, assuming a difference of 6 ms in the QTc interval in the baseline-adjusted, placebo-corrected changes between the 2 energy drinks (SD=11 ms, 80% power, and α=5%), 29 volunteers would be needed for the study.[25] We planned to enroll 40 participants anticipating ≈25% dropout rate. An intention-to-treat analysis was performed using the last-observation-carried-forward methodology to account for missing data.

A repeated-measures analysis of variance, which assumes a compound symmetry covariance structure, was performed with the main effects of intervention, time, and an interaction of intervention and time (R version 3.5.2). The authors verified that this assumption was a reasonable one for their data. Results of this analyses called for a 2-way analysis of variance for each end point (baseline-adjusted) at each time point, with a post hoc Tukey Honestly Significant Difference (HSD), to assess for differences between the 3 interventions (adjusted for subject variability, however, not adjusted for multiple time points) (Table S1). In addition, the maximum value for each end point within each time frame (30–240 minutes) was identified (referred to as the "maximum" time point) to assess the peak effect because of interindividual variability and was analyzed in the same manner as above. The data were also analyzed using the Bonferroni adjustment, which did not change the interpretation of the study (data not included). Finally, the baseline-adjusted, placebo-corrected changes between drink A and drink B were also compared using the paired *t* test. Data analyses were independently performed by a masked statistician. All QTc data are reported using the Bazett's correction formula unless explicitly stated otherwise. Data are reported as mean±SD except in figures (mean±SE).

Results

Forty-four participants were screened, 40 were randomized, and 34 ultimately included for analysis. Baseline demographics are listed in Table 1. None of the participants were on any medications other than 3 who were on oral contraceptives. Two participants requested a granola bar after 180 minutes and 5 requested a granola bar after 210 minutes (1 requested a bar on 2 of the study days after 210 minutes). On the days of such requests, 3 participants had received drink A, 4 had received drink B, and 1 had received placebo. Data imputation for missing data was performed for <0.7% of the data. Table 2 describes ECG and blood pressure parameters at baseline.

Table 1. Patient Characteristics

Characteristic	Total
Age in y, mean (SD)	22.1 (3.0)
Sex, n (%)	
Male	17 (50)
Female	17 (50)
BMI, n (%)	
<18	1 (2.9)
18 to 24	20 (58.8)
25 to 29	9 (26.5)
>30	4 (11.8)
Race, n (%)	
White	4 (11.8)
Asian	22 (64.7)
Other	8 (23.5)
Caffeine consumption, n (%)*	
Rarely	5 (14.7)
Occasionally	7 (20.6)
Frequently	16 (47.1)
Daily	6 (17.6)

BMI indicates body mass index.
*Rare caffeine consumers were defined as <1 caffeine containing drink per month, occasional caffeine consumers were defined as 1 to 3 drinks per month, frequent caffeine consumers were defined as 1 to 6 caffeine containing drinks per week, daily caffeine consumers were defined as ≥1 caffeine containing drink per day.

The interaction term of intervention and time was statistically significant for QTcB, QTcF, QT, PR, QRSd, HR, SBP, DBP, cSBP, and cDBP (all P<0.001). When assessing the intervention effect alone, a statistically significant difference was noted in cSBP, cDBP, SBP, and DBP (all P<0.001) while a trend towards significance was observed for QTcB and QTcF (P=0.082 and 0.064 for ANOVA, respectively). There was no statistically-significant difference between interventions in PR, QRSd, QT, and HR. These statistically significant findings warranted further analyses of the interventions at individual time points (Table S1).

Table 3 describes the maximum change from baseline in each intervention across all end points. The maximum change from baseline in QTcB for drink A, drink B, and placebo were +17.9±13.9, +19.6±15.8, and +11.9±11.1 ms, respectively (P=0.005 for ANOVA). The maximum QTcB changes with drink A and drink B were each statistically significantly different from placebo (P=0.037 and 0.006, respectively). The change from baseline in QTcB with drink A and drink B was statistically significantly greater than placebo at 180, 210, and 240 minutes (all P≤0.025) (Figure 1). Two participants (baseline QTcB 401 and 425 ms) had a change from baseline in QTcB interval over 50 ms with drink A and drink B. In

Table 2. Baseline Cardiovascular Parameters (n=34)

Cardiovascular Parameters	Drink A	Drink B	Placebo
HR, bpm	63.5 (8.2)	63.2 (10.0)	62.5 (7.2)
PR, ms	158.0 (17.1)	157.9 (20.2)	156.4 (18.3)
QRSd, ms	92.3 (13.3)	93.1 (14.1)	93.0 (14.2)
QT, ms	403.4 (20.8)	404.5 (20.5)	407.1 (20.3)
QTcB, ms	412.9 (20.9)	412.3 (22.9)	413.7 (18.7)
QTcF, ms	409.8 (16.8)	409.7 (16.1)	411.6 (15.4)
SBP, mm Hg	116.9 (10.0)	118.5 (9.6)	118.2 (9.0)
DBP, mm Hg	73.4 (7.8)	74.2 (8.4)	73.9 (7.9)
cSBP, mm Hg	104.0 (9.4)	105.3 (8.8)	104.8 (7.9)
cDBP, mm Hg	74.4 (8.0)	75.2 (8.4)	74.8 (8.0)

All data reported as mean (SD). cDBP indicates central diastolic blood pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PR, PR interval; QRSd, QRS duration; QT, QT interval; QTcB, Bazett's corrected QT interval; QTcF, Fridericia's corrected QT interval; SBP, systolic blood pressure.

contrast, none of the participants receiving placebo had a change from baseline in QTcB interval over 50 ms. None of the participants had a QTcB or QTcF >500 ms at any point.

The maximum changes from baseline in SBP for drink A, drink B, and placebo were +15.9±5.0, +14.4±4.8, and +9.8±4.8 mm Hg, respectively (P<0.001 for ANOVA) (Table 3). The maximum SBP changes with drink A and drink B were statistically significantly higher from placebo (P<0.001 for both) (Table 3). The change from baseline in SBP with drink A and drink B was statistically significantly higher at all time points (all P≤0.027) (Figure 2) when compared with placebo. Post-dosing SBP was ≥140 mm Hg (and ≤160 mm Hg) in 9, 8, and 2 participants for drink A, drink B, and placebo, respectively.

Table 3. Average Maximum Change in Cardiovascular Parameters (n=34)

	Drink A	Drink B	Placebo	P Value*
ECG parameters†				
QTcB, ms	17.9 (13.9)‡	19.6 (15.8)§	11.9 (11.1)	0.005
QTcF, ms	15.0 (11.8)‡	15.2 (11.9)§	6.9 (7.1)	<0.001
QT, ms	18.4 (17.0)‡	15.8 (13.3)	10.2 (12.2)	0.026
PR, ms	5.4 (6.5)	6.1 (7.5)	8.6 (6.6)	0.076
QRSd, ms	6.2 (3.3)	5.9 (3.0)	5.0 (2.9)	0.164
HR, bpm	7.7 (7.4)	7.2 (6.8)	7.4 (5.9)	0.918
Hemodynamics†				
SBP, mm Hg	15.9 (5.0)‡	14.4 (4.8)§	9.8 (4.8)	<0.001
DBP, mm Hg	9.6 (4.1)‡	9.6 (4.9)§	6.1 (3.8)	<0.001
cSBP, mm Hg	11.1 (4.7)‡	10.1 (4.8)§	6.5 (3.5)	<0.001
cDBP, mm Hg	9.9 (4.2)‡	9.8 (5.1)§	6.7 (3.5)	<0.001

All data reported as mean (SD). cDBP indicates central diastolic blood pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PR, PR interval; QRSd, QRS duration; QT, QT interval; QTcB, Bazett's corrected QT interval; QTcF, Fridericia's corrected QT interval; SBP, systolic blood pressure.
*P value for analysis of variance adjusted for subject variability.
†No statistically significant difference was noted between drink A and drink B for any parameter.
‡Statistically significant difference between drink A and placebo.
§Statistically significant difference between drink B and placebo.

The maximum change from baseline in QT, DBP, cSBP, cDBP for drink A, drink B, and placebo were also significantly different (all P≤0.026 for ANOVA) (Table 3). The maximum change from baseline for the PR interval, QRSd, and HR, were not significantly different (all P≥0.076 for ANOVA) (Table 3).

The maximum baseline-corrected, placebo-adjusted change in QTcB with drink A was +6.1±15.0 ms compared with +7.7±16.4 ms with drink B (P=0.337). The maximum baseline-corrected, placebo-adjusted change in SBP with drink A was +6.1±5.5 mm Hg compared with +4.6±5.0 mm Hg with drink B (P=0.151). Similarly, the maximum baseline-corrected, placebo-adjusted changes for all other ECG and hemodynamic end points were not different when comparing drink A and drink B (all P≥0.151). The supplement table lists the average change from baseline for each end point across the different time points.

Discussion

To our knowledge, this is the largest, controlled study, indicating acute-consumption of 32 oz of a caffeinated energy drink significantly prolongs the QTc interval when compared with placebo. According to the Food and Drug Administration, QTc prolongation is a well-established risk factor for arrhythmias, with a prolongation over 10 ms prompting further investigation.[26,27] Clinically, a QT/QTc interval >500 ms or a change >30 ms warrants careful monitoring.[28] Drugs such as ranolazine and terfenadine carry warnings, or have been removed from the market because of prolongation of the mean QT/QTc by 6 ms.[29,30]

Three smaller studies have evaluated the impact of consuming 32 oz of energy drinks on heart rhythm variables.[19,25,31] In a non-controlled study (n=14) by Kozik et al, 57% of the healthy participants had a QTc >500 ms after consuming 32 oz of the energy drink.[31] In a small (n=18) randomized, caffeine-controlled clinical trial, 32 oz of an energy drink resulted in a significantly higher QTc at 2 hours when compared with the caffeinated control (+0.4±18.4 ms versus −10.4±14.8 ms, respectively; P=0.02).[19] In another similar placebo-controlled trial (n=27), the QTc interval was transiently higher (6 ms) at 2 hours after 32-oz energy drink consumption when compared with placebo (+3.4±10.7 and −3.2±11.8 ms, respectively; P=0.030).[25] The results of our study confirm these previous findings and suggest that the QTc changes are generally sustained over the 4 hour

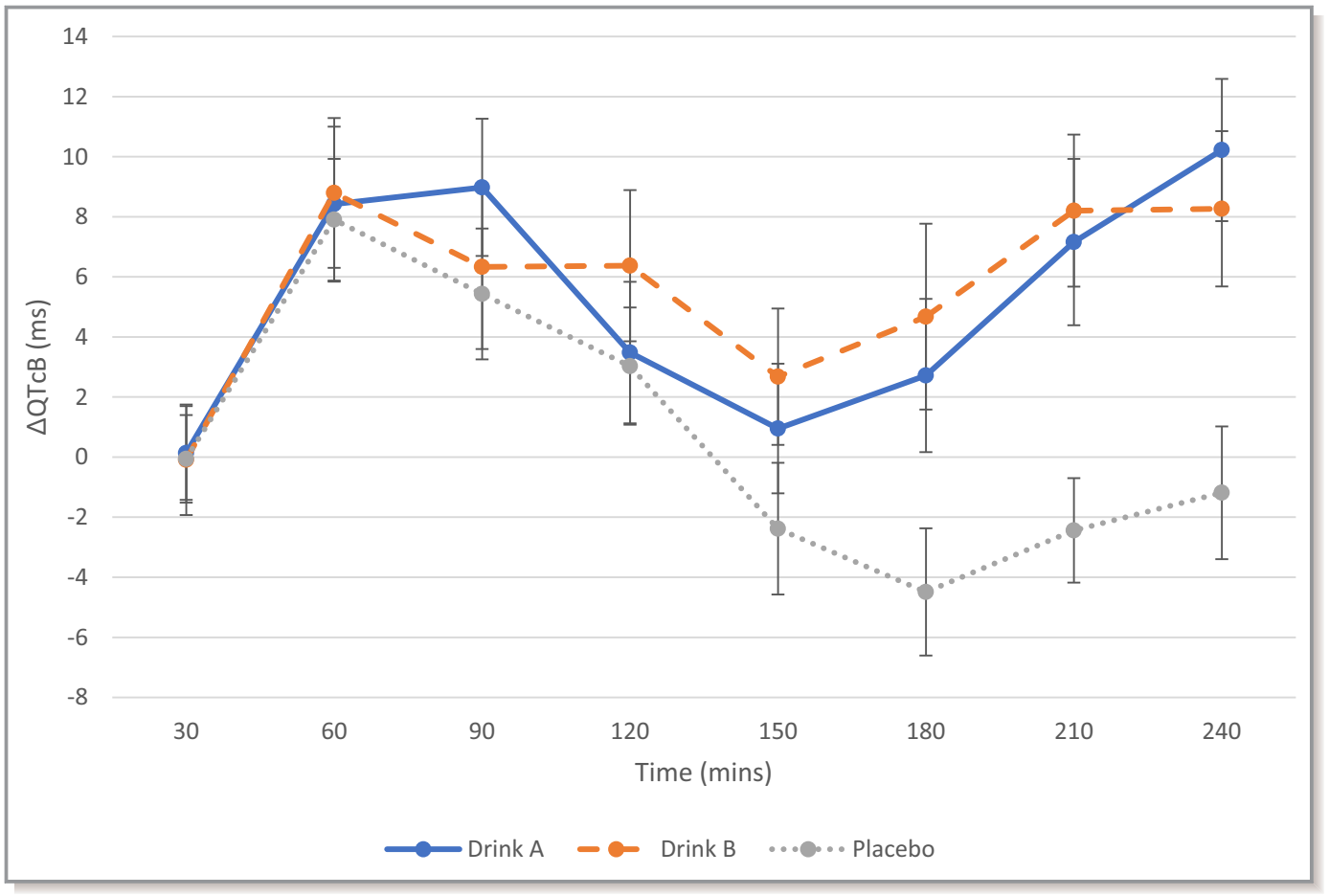

Figure 1. Change in QTcB from baseline over time. QTcB indicates Bazett's corrected QT interval.

monitoring period versus being a transient effect after 32-oz energy drink consumption.

The results are inconsistent in other studies where energy drink volumes under 32 oz were investigated. Brothers et al (n=15) reported no changes in the QTc over 6.5 hours post-consumption of a 24-oz energy drink.[22] Tauseef et al found QTc prolongation of 13 ms after 500 mL (16.9 ounce) energy drink consumption.[20] An Australian study enrolled patients with congenital long QT-syndrome (n=24) and found no statistically significant changes within 90 minutes after consumption of 500 mL (16.9 ounce) of an energy drink. However, 3 patients did have a QTc increase >50 ms when compared with baseline.[23] One parallel designed study assessed the impact of consuming 460 mL of 3 different types of caffeinated energy drinks on ECG parameters with no clinically significant changes.[32]

In this study, both energy drinks had a similar effect on electrocardiographic parameters. Common ingredients contained in this study's products included a combination of caffeine, taurine, glucuronolactone, and B-vitamins. Caffeine at doses under 400 mg is not expected to induce any electrocardiographic changes.[33] Taurine is an endogenous molecule and supplementation is believed to be anti-arrhythmic rather than pro-arrhythmic.[34,35] In animal models evaluating short QT syndrome, a taurine-magnesium coordination compound has been shown to prolong the QT interval in a dose-dependent manner.[36] Data on glucuronolactone and B-vitamins are limited but they are typically regarded as safe.[37] Although the preponderance of data suggest these ingredients may be safe individually, their use in combination requires evaluation.

There was an ≈5 and 4 mm Hg increase in SBP and DBP, respectively after energy drink consumption relative to placebo. A previous meta-analysis of 15 studies including >300 participants similarly suggested a 4- and 3-mm Hg change in SBP and DBP independent of dose.[18] An emerging predictor of cardiovascular risk is cSBP.[38] In this study, cSBP was significantly elevated after energy drink consumption but the long-term consequences remain unknown.

While blood pressure changes can be attributed primarily to the caffeine, other ingredients in energy drinks may pose some hemodynamic activity.[37] Taurine has been shown to lower blood pressure in prehypertensive patients, indicating the need for investigating simultaneous caffeine and taurine intake.[39]

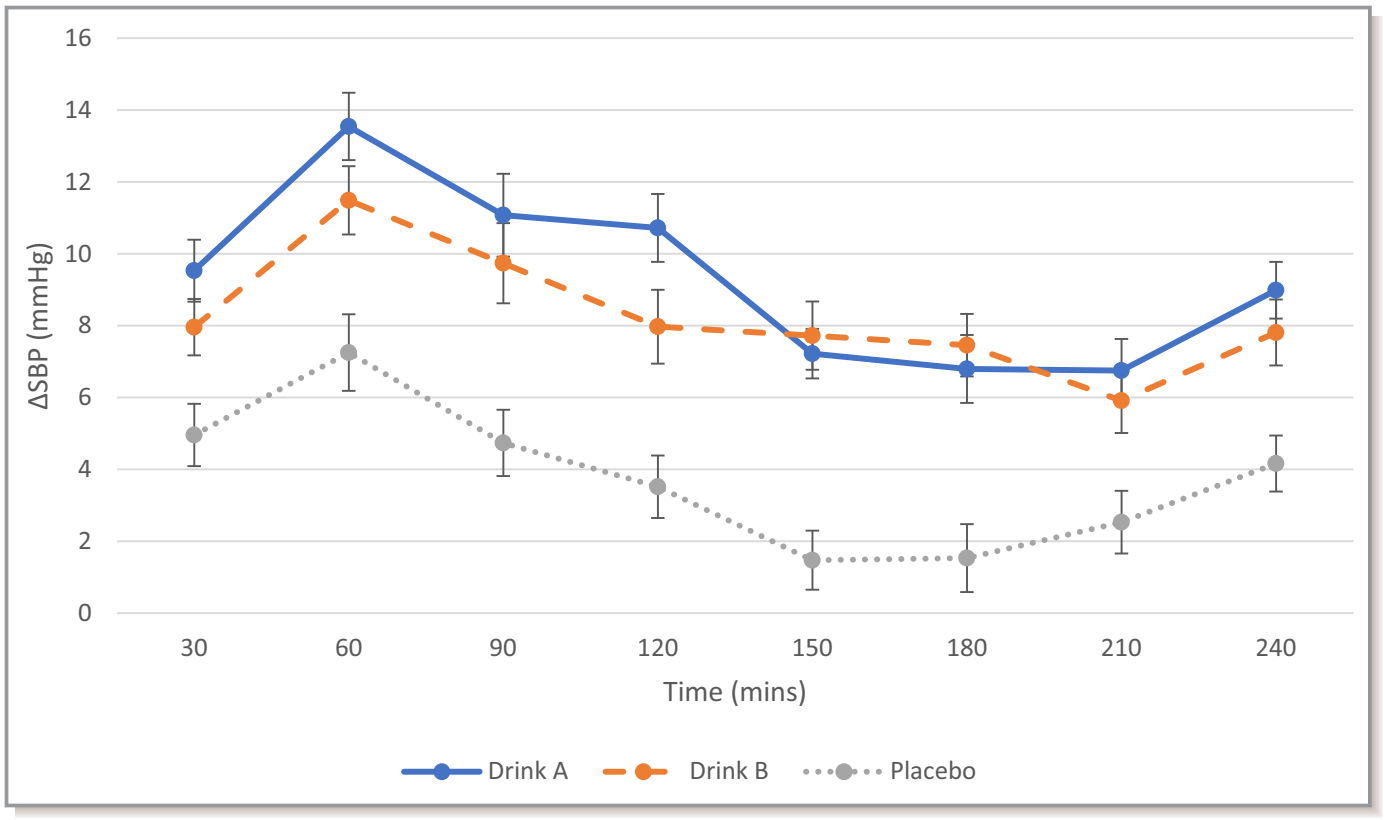

Figure 2. Change in SBP from baseline over time. SBP indicates systolic blood pressure.

Caffeine and ephedra-containing supplements were withdrawn from market after discovery of adverse QTc interval effects.[40] Additionally, a sustained elevation in SBP of 2 mm Hg is associated with a 7% increased risk of mortality from ischemic heart disease and a 10% increased risk of stroke mortality.[41] The cardiovascular effects seen in this study warrant concern as the observation of increased cardiovascular adverse effects and fatalities related to energy drinks remains an important public health issue.[42]

Several factors may limit the generalizability of this study. We did not investigate the effects of different doses and the volume of drink consumed (two 16-ounce cans over 60 minutes) in this study may not be representative of real-world consumption patterns. However, 24-oz variants of certain energy drink brands are readily available, facilitating consumption of larger volumes of energy drink in one sitting. In a survey of 2040 respondents, 16% reported having once consumed >2 energy drinks in a day.[43] We assessed the effects of acute consumption of an energy drink <4 hours, which does not lend insight to long-term effects nor the effects of chronic consumption. Additionally, we assessed energy drink consumption alone, and it is not uncommon for energy drinks to be consumed in combination with other substances such as alcohol.[44,45] While all products were packaged identically, it is possible that some participants were able to identify the energy drink or placebo drinks based on taste or pharmacodynamic response. Our study included only healthy individuals between the ages of 18 to 40 years and results may not be applicable to populations with concomitant comorbidities or those who are not within the studied age range. We did not independently test the concentrations of the ingredients in the energy drinks but relied on publicly available data.

Significant prolongation in the QT interval was also evident within the first hour after energy drink consumption but these are thought to be HR related changes. There appears to be a mild PR shortening effect and is currently thought to be clinically non-significant. Most previous studies used the Bazett's correction formula, but it is known to under correct at low heart rates.[46] Conversely, the Fridericia formula has been shown to be an acceptable alternate correction formula when compared with the Bazett's.[47] Our results are significant regardless of the heart rate correction formula used (Bazett's or Fridericia's). However, it is important to note that QTc prolongation does not necessitate onset of torsades de pointes and is simply a risk factor. While our study incorporates many aspects of a "Thorough QT/QTc Study", assay-sensitivity could not be assessed due to the lack of a positive-control (eg, moxifloxacin).[27]

Individuals with acquired or congenital long QT syndrome and those with hypertension should be more vigilant and limit their energy drink intake. Based on currently available data,

the class of energy drinks, rather than one particular product, warrants use with caution.

Conclusions

Caffeinated energy drinks significantly prolong the QTc interval and raise brachial and central blood pressure post-acute exposure. Further investigation is warranted on whether an individual ingredient or a unique combination leads to the observed electrophysiological and hemodynamic changes. The impact of long-term energy drinks consumption remains unknown.

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Disclosures

Dr. Shah has served as an expert witness in legal cases related to caffeinated energy drinks. The remaining authors have no relevant disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Average Change in All Parameters at Each Time Point

Parameter[§]	Drink A	Drink B	Placebo	*P* value[*]
QTcB, ms				
30 mins	0.1 (9.1)	-0.1 (10.7)	-0.1 (8.5)	0.99
60 mins	8.4 (15.0)	8.8 (14.5)	7.9 (11.8)	0.93
90 mins	9.0 (13.3)	6.3 (16.0)	5.4 (12.7)	0.32
120 mins	3.5 (13.7)	6.4 (14.7)	3.0 (11.4)	0.33
150 mins	1.0 (12.6)	2.7 (13.2)	-2.4 (12.8)	0.06
180 mins	2.7 (14.9)[†]	4.7 (18.0)[‡]	-4.5 (12.3)	<0.01
210 mins	7.2 (16.1)[†]	8.2 (14.8)[‡]	-2.4 (10.1)	<0.001
240 mins	10.2 (13.8)[†]	8.3 (15.1)[‡]	-1.1 (12.9)	<0.001
Max	17.9 (13.9)[†]	19.6 (15.8)[‡]	11.9 (11.1)	<0.01
QTcF, ms				
30 mins	1.0 (5.8)	1.4 (8.1)	-0.6 (5.7)	0.32
60 mins	5.4 (9.2)	6.2 (9.7)	2.5 (7.7)	0.07
90 mins	3.8 (8.1)	3.0 (9.6)	-0.1 (9.2)	0.05
120 mins	-0.6 (8.7)	1.9 (8.6)	-1.5 (8.6)	0.10
150 mins	-1.5 (8.5)	-0.6 (8.5)	-4.0 (9.0)	0.11
180 mins	2.0 (10.2)[†]	3.6 (14.0)[‡]	-3.8 (9.1)	<0.01
210 mins	7.8 (13.9)[†]	8.2 (10.9)[‡]	-0.7 (7.7)	<0.001
240 mins	12.3 (12.5)[†]	9.7 (12.0)[‡]	1.0 (9.5)	<0.001
Max	15.0 (11.8)[†]	15.2 (11.9)[‡]	6.9 (7.1)	<0.001
QT, ms				
30 mins	2.8 (9.3)	4.2 (10.7)[‡]	-1.4 (11.3)	0.03
60 mins	-0.5 (12.4)[†]	1.0 (11.9)[‡]	-7.8 (11.1)	<0.01

90 mins	-5.9 (14.3)	-3.7 (10.1)	-10.5 (12.7)	0.07
120 mins	-8.6 (14.0)	-7.0 (12.6)	-10.5 (12.9)	0.58
150 mins	-6.4 (12.8)	-7.3 (11.9)	-7.1 (12.6)	0.96
180 mins	0.3 (13.6)	1.0 (15.9)	-2.4 (13.8)	0.55
210 mins	8.9 (19.6)	8.0 (13.9)	2.5 (14.3)	0.15
240 mins	16.1 (18.3)†	12.0 (14.0)	5.3 (11.5)	<0.01
Max	18.4 (17.0)†	15.8 (13.3)	10.2 (12.2)	0.03
PR, ms				
30 mins	1.7 (6.4)†	2.2 (6.0)	5.1 (6.2)	0.03
60 mins	1.4 (8.8)	3.5 (8.3)	4.9 (8.0)	0.10
90 mins	-2.2 (8.6)†	-0.7 (7.6)	3.5 (7.3)	<0.01
120 mins	-2.3 (9.0)	-2.0 (8.7)	0.2 (7.2)	0.33
150 mins	-4.9 (9.8)	-3.0 (7.2)	-1.2 (6.1)	0.10
180 mins	-5.0 (9.3)	-5.2 (6.1)	-2.7 (6.0)	0.24
210 mins	-8.7 (9.7)†	-7.9 (7.4)‡	-2.7 (6.7)	<0.01
240 mins	-7.0 (8.5)	-7.7 (7.1)‡	-3.4 (6.9)	0.04
Max	5.4 (6.5)	6.1 (7.5)	8.6 (6.6)	0.08
QRSd, ms				
30 mins	3.8 (3.5)	3.0 (2.7)	3.1 (3.0)	0.37
60 mins	5.0 (3.5)	4.5 (3.8)	3.9 (3.2)	0.35
90 mins	4.0 (3.8)	3.0 (3.4)	2.8 (3.0)	0.16
120 mins	2.3 (3.0)	1.3 (3.6)	1.5 (3.5)	0.28
150 mins	0.9 (4.0)	1.0 (3.5)	0.3 (3.9)	0.64
180 mins	1.9 (3.8)†	0.6 (3.0)	-0.5 (3.4)	0.01
210 mins	2.4 (3.5)†	1.8 (3.7)‡	-0.3 (3.4)	<0.01

240 mins	2.6 (3.8)†	1.7 (2.8)‡	-0.3 (2.9)	<0.01
Max	6.2 (3.3)	5.9 (3.0)	5.0 (2.9)	0.16
HR, bpm				
30 mins	-0.8 (4.2)	-1.4 (4.6)	0.6 (4.9)	0.10
60 mins	3.0 (7.9)	2.3 (6.4)	5.2 (6.2)	0.07
90 mins	5.2 (8.4)	3.0 (7.1)	5.2 (6.3)	0.23
120 mins	4.0 (7.9)	4.0 (7.6)	4.3 (5.7)	0.95
150 mins	2.4 (6.9)	2.9 (6.4)	1.6 (5.8)	0.63
180 mins	0.6 (7.2)	0.8 (6.7)	-0.5 (5.6)	0.62
210 mins	-0.6 (7.4)	0.1 (6.8)	-1.3 (5.3)	0.60
240 mins	-1.9 (6.5)	-1.4 (5.5)	-1.8 (5.2)	0.92
Max	7.7 (7.4)	7.2 (6.8)	7.4 (5.9)	0.92
SBP, mmHg				
30 mins	9.5 (5.0)†	8.0 (4.6)‡	5.0 (5.0)	<0.01
60 mins	13.5 (5.5)†	11.5 (5.5)‡	7.3 (6.2)	<0.001
90 mins	11.1 (6.7)†	9.7 (6.5)‡	4.7 (5.4)	<0.001
120 mins	10.7 (5.5)†	8.0 (6.0)‡	3.5 (5.0)	<0.001
150 mins	7.2 (4.0)†	7.7 (5.5)‡	1.5 (4.8)	<0.001
180 mins	6.8 (5.5)†	7.5 (5.1)‡	1.5 (5.5)	<0.001
210 mins	6.8 (5.1)†	5.9 (5.2)‡	2.5 (5.1)	<0.001
240 mins	9.0 (4.6)†	7.8 (5.4)‡	4.2 (4.5)	<0.001
Max	15.9 (5.0)†	14.4 (4.8)‡	9.8 (4.8)	<0.001
DBP, mmHg				
30 mins	4.5 (4.7)†	4.5 (4.4)‡	1.7 (4.2)	0.01
60 mins	6.9 (4.2)†	6.8 (5.3)‡	2.8 (3.9)	<0.001

90 mins	6.4 (4.6)†	5.5 (4.6)‡	2.2 (4.2)	<0.001
120 mins	5.8 (4.3)†	5.2 (3.9)‡	1.2 (3.1)	<0.001
150 mins	5.5 (4.5)†	6.1 (5.1)‡	1.1 (4.0)	<0.001
180 mins	4.6 (5.9)†	4.3 (6.1)‡	0.8 (3.8)	<0.001
210 mins	1.4 (5.1)	2.7 (5.2)	1.1 (3.9)	0.28
240 mins	3.0 (4.6)	3.3 (5.3)	2.4 (4.6)	0.69
Max	9.6 (4.1)†	9.6 (4.9)‡	6.1 (3.8)	<0.001
cSBP, mmHg				
30 mins	6.6 (5.2)†	5.7 (4.9)‡	2.8 (4.2)	<0.01
60 mins	8.9 (5.2)†	7.4 (5.6)‡	3.2 (4.6)	<0.001
90 mins	6.8 (5.9)†	5.5 (5.5)‡	1.7 (5.2)	<0.001
120 mins	6.4 (5.1)†	4.6 (5.3)‡	0.7 (3.9)	<0.001
150 mins	4.6 (3.8)†	4.7 (5.3)‡	-0.5 (4.5)	<0.001
180 mins	4.0 (4.8)†	4.6 (5.3)‡	-0.6 (4.7)	<0.001
210 mins	2.9 (4.5)	3.3 (5.2)‡	0.6 (4.8)	0.02
240 mins	4.9 (4.6)†	4.1 (5.0)	1.9 (4.7)	0.02
Max	11.1 (4.7)†	10.1 (4.8)‡	6.5 (3.5)	<0.001
cDBP, mmHg				
30 mins	4.6 (4.6)†	4.5 (4.7)	2.1 (4.2)	0.03
60 mins	7.6 (4.3)†	6.9 (5.3)‡	3.4 (3.8)	<0.001
90 mins	7.0 (5.1)†	6.0 (4.9)‡	2.9 (4.2)	<0.001
120 mins	6.3 (4.6)†	5.8 (4.1)‡	2.0 (3.2)	<0.001
150 mins	5.5 (4.4)†	6.2 (5.3)‡	1.6 (4.1)	<0.001

180 mins	4.6 (6.0)†	4.1 (6.4)‡	1.2 (3.7)	<0.01
210 mins	1.5 (5.2)	2.7 (5.2)	1.3 (4.0)	0.34
240 mins	3.0 (4.5)	3.3 (5.3)	2.6 (4.5)	0.81
Max	9.9 (4.2)†	9.8 (5.1)‡	6.7 (3.5)	<0.001

All data reported as mean (standard deviation). cDBP, central diastolic blood pressure; DBP, diastolic blood pressure; cSBP, central systolic blood pressure; HR, heart rate; PR, PR interval; QRSd, QRS duration; QT, QT interval; QTcB indicates Bazett's corrected QT interval; QTcF, Fridericia's corrected QT interval; SBP, systolic blood pressure.

*$P<0.05$ for analysis of variance adjusted for subject variability

†Statistically significant difference between Drink A and Placebo

‡Statistically significant difference between Drink B and Placebo

§No statistically significant difference was noted between Drink A and Drink B for any parameter