

Randomized Controlled Trial of High-Volume Energy Drink Versus Caffeine Consumption on ECG and Hemodynamic Parameters

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Background—Caffeine in doses <400 mg is typically not considered arrhythmogenic, but little is known about the additional ingredients in energy drinks. We evaluated the ECG and blood pressure (BP) effects of high-volume energy drink consumption compared with caffeine alone.

Methods and Results—This was a randomized, double-blind, controlled, crossover study in 18 young, healthy volunteers. Participants consumed either 946 mL (32 ounces) of energy drink or caffeinated control drink, both of which contained 320 mg of caffeine, separated by a 6-day washout period. ECG, peripheral BP, and central BP measurements were obtained at baseline and 1, 2, 4, 6, and 24 hours post study drink consumption. The time-matched, baseline-adjusted changes were compared. The change in corrected QT interval from baseline in the energy drink arm was significantly higher than the caffeine arm at 2 hours (0.44 ± 18.4 ms versus -10.4 ± 14.8 ms, respectively; $P=0.02$). The QTc changes were not different at other time points. While both the energy drink and caffeine arms raised systolic BP in a similar fashion initially, the systolic BP was significantly higher at 6 hours when compared with the caffeine arm (4.72 ± 4.67 mm Hg versus 0.83 ± 6.09 mm Hg, respectively; $P=0.01$). Heart rate, diastolic BP, central systolic BP, and central diastolic BP showed no evidence of a difference between groups at any time point. Post energy drink, augmentation index was lower at 6 hours.

Conclusions—The corrected QT interval and systolic BP were significantly higher post high-volume energy drink consumption when compared with caffeine alone. Larger clinical trials validating these findings and evaluation of noncaffeine ingredients within energy drinks are warranted.

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There are currently more than 500 energy drink products available on the market purported to boost physical and mental alertness.¹ In line with their increased popularity is a coinciding rise in energy drink–associated emergency department visits and deaths, which has led to questions about their true safety profile.^{2–4} In a review of energy drink–associated adverse cardiovascular events, abnormal heart rhythms such as atrial and ventricular fibrillation, ST elevation, and QT

prolongation have been reported.⁵ However, the exact relationship between energy drinks and these adverse events has gone primarily unexplained.

Energy drinks usually consist of caffeine plus proprietary energy blends that vary between products. Caffeine has been around for centuries and is generally recognized as safe in doses less than 400 mg by the Food and Drug Administration.⁶ Caffeine, a natural methylxanthine, acts as a central nervous stimulant in humans by antagonizing adenosine receptors, leading to additional cardiovascular effects such as peripheral vasoconstriction and subsequent increased blood pressure (BP).^{7,8} Caffeine alone is not suspected to induce any ECG changes in healthy volunteers at a dose of 400 mg.⁹ Typically, caffeine toxicity–related adverse events have only been observed in case studies where doses far exceed 400 mg.^{10,11}

Although the cardiovascular safety profile of caffeine has been relatively well established, there is little published literature on the electrophysiologic and hemodynamic changes with multi-ingredient energy drinks. We conducted a randomized controlled trial assessing the cardiovascular safety of high-volume energy drink consumption.

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Methods

Study Oversight and Patient Population

The protocol and informed consent forms were approved by the David Grant Medical Center Institutional Review Board (protocol No. FDG20130042H). All participants provided written informed consent.

Participants were recruited via email and flyers between 2013 and 2014 on a US Air Force Base installation. Healthy volunteers between the ages of 18 and 40 years were included. Participants were excluded if they had a current or previous diagnosis of abnormal heart rhythm, a BP >140/90 mm Hg, any comorbid medical conditions, history of substance abuse, renal or hepatic dysfunction, concurrent use of drugs or over-the-counter products that may interact with study drinks or affect ECG or BP parameters (excluding oral contraceptives), or were pregnant or lactating.

Study Design

This was a randomized, double-blind, caffeine-controlled, crossover study in healthy adults. Using a computer-generated randomization code, participants were assigned to consume either a 1-time 32-ounce (946 mL) dose of a commercially available energy drink (containing 108 g of sugar, vitamin B2, vitamin B3, vitamin B6, and vitamin B12, and a proprietary energy blend of taurine, panax ginseng extract, L-carnitine, caffeine [320 mg], glucuronolactone, inositol, guarana extract, and maltodextrin) or a matching 32-ounce (946 mL) control drink containing 320 mg of caffeine, 40 mL of lime juice, and 140 mL of cherry syrup in carbonated water (Figure 1). Other than the caffeine, all

added ingredients in the control group were expected to have no impact on any end points and were simply added to match the active drink. The dose was based on the observation that cardiovascular adverse effects typically occur with high consumption of energy drink/caffeine.⁵ The amount of energy drink participants were asked to consume (2 cans totaling 320 mg caffeine) correlates to the average daily caffeine consumption (300 mg) of the US population.¹² Further, nearly 15% of military personnel consume 3 cans a day in the deployed setting, which may predispose them to a higher risk threshold.^{5,13} After a minimum 6-day washout period, participants proceeded to consume the alternate study drink. Participants were required to fast for 12 hours, and abstain from any caffeinated products 48 hours prior to each study day and throughout the 24-hour follow-up period. All study drinks were presented in identical containers and were consumed over a 45-minute period. End points were measured on each study day at baseline (immediately prior to study drink consumption), and 1, 2, 4, 6, and 24 hours post consumption of study drink. Due to the possibility of circadian rhythm changes, the start time for each patient was approximately the same on the 2 study days (maximum difference ≤ 80 minutes).

End Points and Assessments

The primary end point was the QTc interval. Secondary end points were uncorrected QT interval, PR interval, QRS duration, heart rate (HR), peripheral systolic BP (pSBP), peripheral diastolic BP (pDBP), central systolic BP (cSBP), central diastolic BP (cDBP), and augmentation index (AI). Participants were also asked to describe any adverse events they were experiencing at each time point.

A 12-lead ECG (Philips PageWriter Trim III, Philips Medical Systems, Andover, MA) was obtained with the participant in the supine position. The machine was calibrated to a 1-mV/cm standardization with a paper speed of 25 mm/s. Peripheral BP measurements were obtained in duplicate after a 5-minute rest using a standard automated vital signs monitor (Masimo SET Vital Sign Monitor; Welch Allyn; Skaneateles Falls, NY). Central BP measurements were obtained using the SphygmoCor PWA system (AtCor Medical Pty Ltd, West Ryde, Australia). SphygmoCor is a validated system that uses applanation tonometry to noninvasively translate a radial pressure waveform taken at the wrist to an aortic pressure waveform. AI was corrected to a HR of 75 beats per minute.

Statistical Analysis

Based on some of our previous data, we expected a change in the energy drink arm of 10 ms and no change in the caffeine control arm. To detect a between-group difference of 10 ms

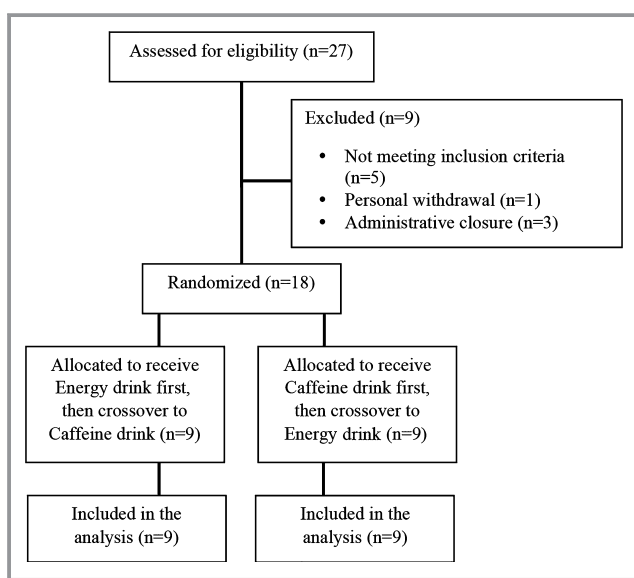


Figure 1. CONSORT flow diagram.

and assuming an SD of 14 ms (2-sided $\alpha=5\%$ and 80% power), we would need 18 participants for the study. The time-matched changes from baseline were compared between the energy drink and control arms using the Wilcoxon signed rank test. All data were reported as mean \pm SD unless otherwise stated. Applanation tonometry requires operator proficiency and only those with an operator index of 70% or greater were included. Intention-to-treat analysis using the last-observation-carried-forward methodology was performed to account for the missing values.

Results

Baseline Characteristics

Twelve men and 6 women ($n=18$) were included, of which 11 identified as white, 3 as Asian, 2 as Hispanic, 1 as black, and 1 undisclosed. Average age, height, and weight were 26.7 ± 4.0 years, 171.9 ± 12.2 cm, and 74.4 ± 15.0 kg, respectively. Nine were regular coffee drinkers (≥ 1 cup of coffee per day), 5 were occasional drinkers, and 4 reported no coffee consumption. Four reported regular energy drink use (≥ 1 can per day), 5 occasional energy drink use, and 9 no energy drink use. Data imputation was performed for less than 4% of central BP parameters. At each time point, the change from baseline is reported in Table 1.

Baseline QTc interval, uncorrected QT interval, PR interval, QRS duration, and HR were 413 ± 17.3 ms, 405 ± 26.9 ms, 158 ± 21.0 ms, 89.1 ± 9.69 ms, and 63.4 ± 10.5 beats per minute, respectively. Baseline pSBP, pDBP, cSBP, cDBP, and AI were 117 ± 9.89 mm Hg, 72.0 ± 8.56 mm Hg, 103 ± 9.00 mm Hg, 73.4 ± 8.60 mm Hg, and 5.50 ± 10.1 , respectively.

ECG Effects

A significant difference in the baseline-adjusted QTc interval (Figure 2) was evident 2 hours after energy drink consumption when compared with caffeine (0.44 ± 18.4 ms versus -10.4 ± 14.8 ms, respectively; $P=0.02$). There was no evidence of a statistically significant difference in the baseline-adjusted HR 2 hours after energy drink consumption when compared with caffeine (3.39 ± 11.04 versus -0.61 ± 9.13 , respectively; $P=0.07$). There was no evidence of time-matched intragroup differences with QT interval, PR interval, and QRS duration (all $P>0.14$).

Blood Pressure Effects

A significant difference in baseline-adjusted pSBP (Figure 3) was evident 6 hours after energy drink consumption when compared with the caffeine arm (4.72 ± 4.67 mm Hg versus 0.83 ± 6.09 mm Hg, respectively; $P=0.01$). A significant

decrease in baseline-adjusted AI was evident 6 hours post energy drink when compared with the caffeine arm (-3.72 ± 7.61 versus 1.50 ± 9.85 ; $P=0.02$). No evidence of difference was seen with pDBP, cSBP, or cDBP at any time point between the 2 groups (all $P>0.07$).

Adverse Events

Adverse effects were experienced by 15 participants during the energy drink arm and by 13 participants during the caffeine control arm (Table 2). Adverse events included anxiety, difficulty in falling asleep, dizziness, dyspepsia/upset stomach, epistaxis, headache, jitteriness, nausea, palpitations, and shortness of breath. These effects were reported throughout the 24-hour monitoring period without a discernable pattern. None of the adverse events caused a discontinuation in study participation.

Discussion

QTc prolongation is a recognized marker of increased risk for fatal arrhythmias. Prolongation of the QT/QTc interval by more than 60 ms from baseline or a value >500 ms is a marker for life-threatening arrhythmias. For this reason, several published studies have assessed QT/QTc effects post energy drink consumption. This is one of the first caffeine-controlled studies that shows significant QTc prolongation of ≈ 10 ms 2 hours after high-volume energy drink consumption in young healthy volunteers. It is possible that previous published studies showed a lack of effect due to studying a lower dose of energy drink (250–750 mL), monitoring for an insufficient amount of time (30–240 minutes), or not having a control arm.^{14–19} It also appears that the product and dose used in our study was different from the other studies, which might explain our significant findings. Our findings are similar to another study ($n=27$), which used the same dose as ours and found a significant 6-ms prolongation in QTc at 2 hours when compared with placebo.²⁰ Further, in a noncontrolled study ($n=14$) using the same dose (2 cans) as in our study, 57% of participants had a QTc >500 ms post consumption.²¹ In contrast, a study by Brothers et al²² ($n=15$), comparing low- and moderate-dose energy drinks, coffee, and water, found no changes in the QTc interval.

The Food and Drug Administration requires a thorough investigation of QT/QTc effects for all new drug entities, with a prolongation over 10 ms prompting regulatory concern.²³ Cisapride and other noncardiovascular drugs have been withdrawn from the market because of a 5- to 10-ms QT interval prolongation.²⁴ Ephedra-containing dietary supplements were also pulled from the market partly because of their association with significant QTc interval prolongation.²⁵

Table 1. Baseline-Adjusted ECG and BP Parameters

	Drink	1 Hour	2 Hours	4 Hours	6 Hours	24 Hours
QTc, ms	ED	-1.17±20.7	0.44±18.4	0.83±19.5	-1.33±17.4	1.44±18.3
	C	-5.83±17.7	-10.4±14.8	-3.67±13.2	-5.89±15.3	-4.17±17.4
	<i>P</i> value	0.38	0.02*	0.35	0.61	0.47
QT, ms	ED	-2.44±16.3	-10.7±20.3	-3.33±20.7	-1.78±22.6	7.56±27.8
	C	-2.44±17.1	-9.33±18.1	-2.67±18.5	-8.67±19.5	3.78±23.7
	<i>P</i> value	0.782	0.89	0.77	0.17	0.85
PR, ms	ED	-1.78±10.47	-5.11±11.4	-6.00±15.7	-6.22±14.7	0.67±11.7
	C	-3.11±10.2	-2.67±11.4	-4.89±10.9	-4.78±9.43	1.77±10.6
	<i>P</i> value	0.86	0.56	0.82	0.68	0.95
QRS, ms	ED	6.17±3.33	4.22±2.73	3.39±4.15	3.22±5.01	1.94±3.69
	C	6.11±4.91	3.28±3.92	3.06±2.90	1.28±3.82	0.78±4.26
	<i>P</i> value	0.82	0.15	0.60	0.24	0.25
HR, bpm	ED	0.33±10.5	3.39±11.04	1.22±11.6	0.17±12.3	-1.50±12.0
	C	-1.28±8.41	-0.61±9.13	-0.22±8.59	0.61±10.1	-2.28±11.1
	<i>P</i> value	0.33	0.07	0.42	0.82	0.71
pSBP, mm Hg	ED	6.00±6.64	4.28±6.17	3.89±5.4	4.72±4.67	-0.81±4.54
	C	7.08±4.37	4.78±4.55	2.25±5.45	0.83±6.09	-1.33±6.15
	<i>P</i> value	0.77	0.97	0.55	0.01*	1.00
pDBP, mm Hg	ED	4.25±4.01	1.33±3.87	0.28±4.92	1.53±3.70	-0.03±3.76
	C	4.33±4.59	2.72±4.32	1.39±2.77	-0.50±5.85	-1.03±4.65
	<i>P</i> value	0.75	0.37	0.36	0.27	0.40
cSBP, mm Hg	ED	4.28±5.48	2.89±6.03	1.67±5.08	2.28±3.54	-1.44±3.40
	C	3.67±6.11	3.06±4.26	0.33±5.41	-0.33±6.27	-2.00±5.08
	<i>P</i> value	0.78	1.00	0.39	0.08	0.89
cDBP, mm Hg	ED	3.89±3.98	1.50±3.79	-0.06±5.00	1.22±3.44	-0.67±3.56
	C	3.78±4.63	2.17±4.42	1.56±3.33	-0.56±5.71	-1.61±4.17
	<i>P</i> value	0.89	0.67	0.19	0.35	0.58
AI	ED	-2.50±6.48	-1.61±5.70	-3.56±5.67	-3.72±7.61	-2.61±7.21
	C	-0.55±9.39	2.78±9.92	-0.88±9.49	1.50±9.85	2.33±7.18
	<i>P</i> value	0.52	0.11	0.37	0.02*	0.07

AI indicates augmentation index, corrected to a heart rate (HR) of 75 beats per minute (bpm); C, caffeine; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; ED, energy drink; pDBP, peripheral diastolic blood pressure; pSBP, peripheral systolic blood pressure.

**P*<0.05.

Our findings are concerning since caffeine likely does not affect the QTc interval based on previous studies. Further investigation of other energy drink constituents is necessary.⁹

Taurine, L-carnitine, and panax ginseng are some additives found in energy drinks and have conflicting physiologic effects. The preponderance of evidence suggests taurine is more likely an antiarrhythmic than a proarrhythmic.²⁶ A correlation between L-carnitine deficiency and short QT syndrome has been postulated.²⁷ However, L-carnitine supplementation is not suspected to result in an overcorrection

or prolongation of the QT interval based on published literature. Interestingly, panax ginseng, at a dose of 200 mg in one study, showed a transient prolongation of the QTc interval 2 hours after ingestion, but this appears to be a chance finding and not evident in other studies.^{20,28} Due to the fact that multiple ingredients in energy drinks have the ability to alter electrophysiological properties, their sole and concurrent use needs further scrutiny.

The long-term use of energy drinks also needs particular attention. In one study, consuming a single energy shot

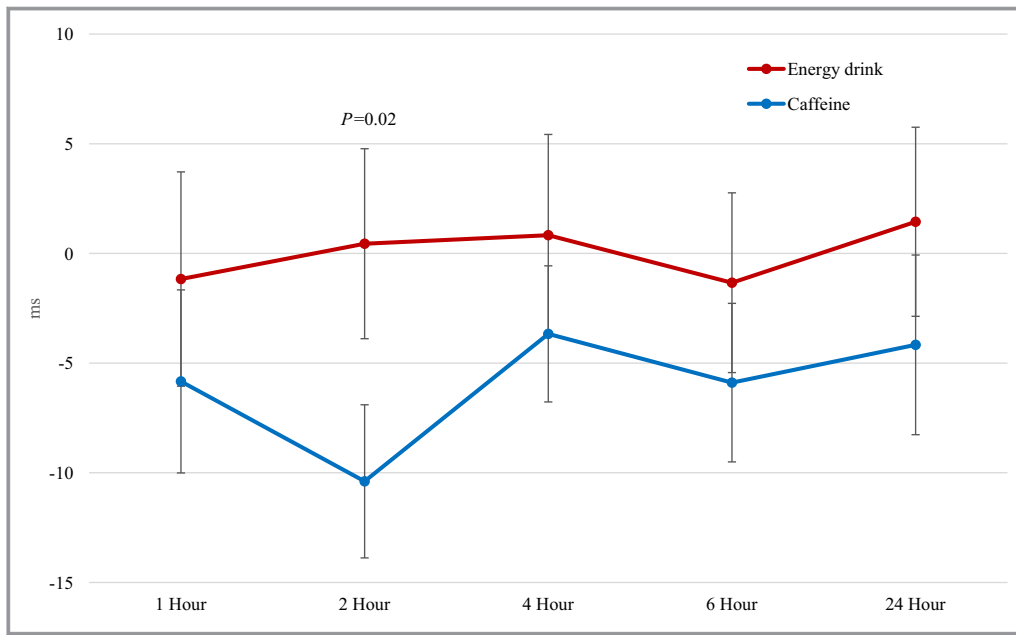


Figure 2. Baseline-adjusted corrected QT interval with energy drink vs caffeine consumption (0.44 ± 18.4 ms vs -10.4 ± 14.8 ms at 2 hours, respectively; $P=0.02$). Data are reported as mean \pm standard error bars.

(60 mL) twice daily for 7 days conferred no significant ECG changes when compared with placebo.²⁹ Similarly, 500 mL of another energy drink consumed for 7 days showed no ECG-related changes from baseline.¹⁵ However, these results cannot be generalized across all energy drink

products. While the degree of BP change seen in our study is generally not concerning in an acute setting, even mild sustained elevations in systolic BP at the population level can increase the risk of adverse cardiovascular outcomes.^{30,31}

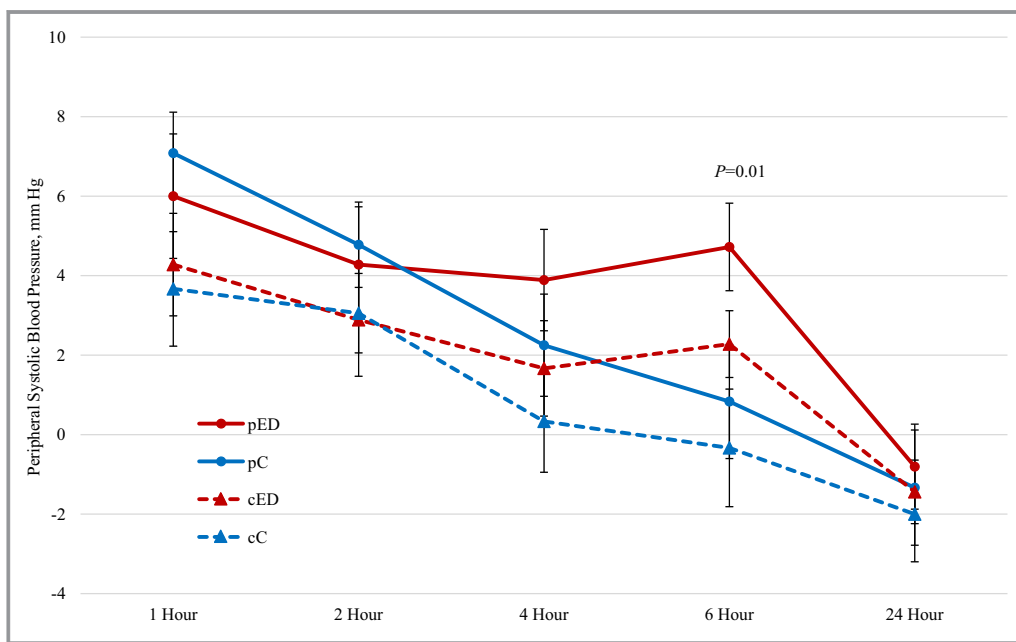


Figure 3. Baseline-adjusted peripheral systolic blood pressures with energy drink (pED) and caffeine (pC) consumption (4.72 ± 4.67 mm Hg vs 0.83 ± 6.09 mm Hg at 6 hours, respectively; $P=0.01$). Baseline-adjusted central systolic blood pressure measurements with energy drink (cED) vs caffeine (cC) consumption. Data are reported as mean \pm standard error bars.

Table 2. Adverse Events Reported

Adverse Event	Energy Drink (n=18), No. (%)	Caffeine (n=18), No. (%)
Any side effect	15 (83)	13 (72)
Anxiety	3 (17)	5 (28)
Difficulty in falling asleep	4 (22)	2 (11)
Dizziness	3 (17)	2 (11)
Dyspepsia/upset stomach	4 (22)	3 (17)
Epistaxis	1 (6)	1 (6)
Headache	2 (11)	3 (17)
Jitteriness	8 (50)	6 (33)
Nausea	2 (11)	0 (0)
Palpitations	4 (22)	0 (0)
Shortness of breath	1 (6)	1 (6)

In this study, both the energy drink and caffeine arms exhibited a similar increase in pSBP from baseline for the initial 4 hours post study drink consumption. Caffeine is rapidly absorbed and typically peaks at about 1 hour, explaining the initial BP increase in both study arms.³² This is similar to results from another study by Svatikova et al³³ that also suggested activation of the catecholamine pathway. However, the sustained pSBP elevation by ≈ 4 mm Hg at 6 hours post energy drink consumption suggests that other ingredients may be hemodynamically active. Guarana, another common ingredient in energy drinks, may contain 2% to 15% of its dry weight in caffeine.³⁴ This may or may not explain a delayed BP response when compared with caffeine alone.³⁵ Taurine, in contrast, is thought to have a BP-lowering effect at higher doses, potentially altering the overall BP response.³⁶ The current literature is lacking regarding the hemodynamic profile of the ingredients contained in energy drinks, making it difficult to ascertain whether it is caffeine interacting with the other ingredients or the other ingredients alone that are driving the BP effects.

Although not statistically significant, a trend in the elevation of cSBP at 6 hours post energy drink consumption was evident. Central BP indices are emerging as superior predictors of cardiovascular risk over peripheral BPs as they better reflect vascular compliance and should be further investigated in future studies.³⁷ The trend towards a higher HR at 2 hours and the lower AI at 6 hours in the energy drink arm are clinically not critical in this acute setting.

Certain populations may consider exercising caution when consuming energy drinks. Those with congenital long QT syndrome are at a predisposed risk for arrhythmias, particularly torsades de pointes.³⁸ More commonly, those with

acquired long QT syndrome induced by concomitant use of QT/QTc-prolonging drugs, hypokalemia, or hypomagnesaemia are at a similar risk.³⁹ Obesity has also been associated with prolongation of the QT interval.^{40,41} Interestingly, in one noncontrolled study, the cohort with overweight/obese participants (n=18) showed significant QT prolongation from baseline after consuming 5 mL/kg of an energy drink (340 ± 57 ms versus 357 ± 54 ms, $P=0.006$).²⁴ The consumption of energy drinks with alcohol is another practice common in some social settings.⁴² Caution should be exercised as combining alcohol or illicit substances with energy drinks may trigger or exacerbate untoward cardiovascular events.^{43,44}

Study Limitations

Our results should be interpreted with caution due to several limitations. Importantly, our results only appear to be significant relative to the caffeine group, and the change from baseline post energy drinks is not alarming. Of note, the risk of arrhythmia may be negligible because the QTc difference is transient. Currently, we cannot explain the QTc reduction in the caffeine arm. We did not utilize a true placebo arm in this study, which may be critical for future studies. As such, in another study using a noncaffeinated placebo, a mild reduction in QTc was also evident.²⁰ The hemodynamic changes may be benign if not sustained with chronic use. While caffeine alone is not expected to shorten the QTc interval, this possibility cannot be ruled out. We did not control for food intake post baseline measurement on study days. Food intake has been linked to shortening of the QTc interval, which could possibly explain our discordant findings.⁴⁵ We also used the machine-calculated values and did not hand measure the ECG parameters. The latter is considered as the gold standard by some experts. Our results can only be generalized to the time points specified in the study. Consumption of 946 mL (32 ounces) of an energy drink over 45 minutes may not be representative of normal consumption patterns. However, it is important to note that 710-mL (24 ounces) energy drink cans are readily available in the market and it appears that serious adverse events may be associated with a higher volume of consumption.⁴⁶ T-wave peak to T-wave end interval analysis is emerging as a superior marker of arrhythmic risk and future studies should evaluate not only the QT/QTc interval, but also the transmural dispersion of ventricular repolarization to accurately depict energy drink-related arrhythmic risk.⁴⁷ Although our sample size mimics some previous published studies, future studies may need to employ a larger sample size to capture differences in sex or dosing.²⁵ Since this was a proof-of-concept study, we were not powered for multiple comparisons and, as a result, the reported *P* values are not adjusted for multiple comparisons.

Conclusions

Our study findings suggest significant prolongation of the QTc interval 2 hours after energy drink consumption when compared with caffeine. Systolic BP remained significantly elevated over the caffeine control at 6 hours post energy drink consumption. Ingredients contained in energy drinks other than caffeine warrant further investigation. Larger clinical trials controlling for the limitations of this study are warranted.

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Disclosures

None.

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