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The Effect of Energy Drinks on Cardiovascular Variables: A Randomized Controlled Trial

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THE EFFECT OF ENERGY DRINKS ON CARDIOVASCULAR VARIABLES: A RANDOMIZED CONTROLELD TRIAL

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The Effect of Energy Drinks On Cardiovascular Variables: A Randomized Controlled Trial

Abstract

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Many studies have investigated the effects of energy drinks on cardiovascular parameters. These studies were typically conducted with high volume (32 ounces) energy drinks and have demonstrated association with QT prolongation and blood pressure elevation after consumption. Currently, there is inconclusive evidence with lower volume energy drinks. This study intends to evaluate the effects of the largest commercially available energy drink can (24 ounces) in the United States on cardiovascular parameters compared with placebo arm. A randomized, double-blinded, placebo-controlled, crossover trial was conducted over 2 separate days with a minimum of 6-day wash out period. Healthy volunteers between the age of 18 and 40 randomly consumed either a 24 oz energy drink or 24 oz placebo control drink on different days. Subjects were required to fast overnight and refrain from products containing caffeine or alcohol 48 hours prior to each study day. ECG, peripheral and central BP, heart rate, and augmentation index were measured at baseline, 1, 2, 3, and 4 hours post-consumption. Primary endpoints were average maximum change of corrected QT (QTc) interval and peripheral systolic blood pressure (pSBP) from baseline. The study enrolled 20 participants with a mean age of 23±5 years. The maximum baseline-adjusted difference of QTc interval was significantly higher in the energy drink arm than the placebo arm (13.68 ± 12.71 vs 4.20 ± 8.80 ms, respectively, $p = 0.007$). The maximum baseline-adjusted difference of pSBP was significantly higher in the energy drink arm compared

to placebo (11.10 ± 5.24 vs 6.08 ± 7.07 mmHg, respectively; p= 0.006). Maximum baseline-adjusted difference of central diastolic BP and systolic and diastolic BP were also statistically significantly higher in the energy drink arm. This study demonstrated that a single, 24-ounce can of an energy drink can significantly prolong the QTc interval and raise pSBP.

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Background

Energy drinks are beverage products that typically contain caffeine and energy-boosting ingredients. They are widely consumed not only in the United States (US) but also globally. Some energy drinks that are available in the US include Monster®, Red Bull®, 5-hour ENERGY®, and Rockstar® (Grasser 2016). Energy drinks were reported to comprise 60% of US functional beverages' market share, which includes market for sport drinks and nutraceutical beverages, and its market growth have increased by almost 250% between 2004 and 2009 (Heckman 2010). These products have become a regular staple for the young population groups, most notably adolescents, college students, and young working adults, to boost energy and curb fatigue. It has been reported that over 30% of young adults age 18 to 24 years are consuming energy drink regularly (Heckman 2010, O'Brien 2008).

In the past decade, the safety of energy drinks has been examined given several reports of adverse events and even deaths linked to consumption of energy drinks. Most cases reported incidences of arrhythmia after energy drinks consumption, which had led to emergency room visits or deaths (Avci 2013, Israelit 2012, Goldfarb 2014, Malinauskas 2007, SAMHSA 2013, Seifert 2013). Another adverse event that had been reported include the incidence of seizure, which can also lead to serious short-term and long-term consequences (Seifert 2013). As of June 2014, 34 deaths associated with energy drinks had been reported to Food and Drug Administration (FDA), whereas

22 cases were linked to 5-hour ENERGY®, 11 cases to Monster® and 1 case to Rockstar® (CFSAN 2012).

Currently, there is no regulation in place for energy drinks by the FDA as it is categorized as dietary supplements. Most energy drinks contain caffeine as one of the major ingredients. Other common ingredients that can be found in energy drinks include taurine, ginseng, l-carnitine, and yohimbine. Most were claimed to boost physical performance and metabolism. These ingredients have reported adverse effects associated with them listed in **Table 1** (Seifert 2011).

Table 1: List of Energy Drink Ingredients Associated with Adverse Effects

Ingredients	**Reported Adverse Effects**
Caffeine	Anxiety, irritability, insomnia, tachycardia, hypertension, abnormal heart rhythm, palpitation, upset stomach, rigidity
Ginseng	Diarrhea, headache, vertigo, hypertension, hypersensitivity reactions, insomnia, irritability
L-carnitine	Upset stomach, increased seizure risk
Taurine	Lower blood pressure
Yohimbine	Blood pressure fluctuations depending on doses, tachycardia

With questionable safety of energy drinks, there is huge concern regarding the consumption of energy drinks that are available on the market, especially there is currently no regulation in place. Further investigations are warranted to fill the gaps and add knowledge to the general public.

Energy Drink Effects on Cardiovascular Parameters

Energy drinks have been previously investigated in clinical studies, mostly for their effects on cardiovascular parameters including heart rhythm, blood pressure (BP), and heart rate. Several studies have demonstrated significant effect of energy drinks in prolonging QT interval (Basrai 2019, Fletcher 2017, Shah 2019). QT prolongation is an irregular heart rhythm that put

human subjects at risk for life-threatening arrhythmias, most commonly “Torsades de Pointes” (TdP) that can lead to sudden cardiac death (Nachimuthu 2012). The incidence of TdP after taking QT-prolonging substances ranges between 2% and 12% (Tisdale 2016). Prolonged corrected QT (QTc) interval is defined as greater than 450 milliseconds (ms) in males or 470 ms in females. These values are obtained by adjusting the QT interval measurements based on individual’s heart rate. QT prolongation occurs when ventricular repolarization is abnormally prolonged, which can trigger the myocardium to undergo early after depolarization (EAD) before completing the full phases of cardiac action potential. When the EAD reaches a critical threshold, it can prematurely depolarize the ventricles and cause ventricular contraction. Overall, with desynchronization of the action potentials across the myocardium, it can create excitation that can lead to TdP (Nachimuthu 2012).

The most recently published study on energy drink evaluated the cardiovascular effects of two commercially different energy drinks in a randomized, placebo-controlled, crossover trial over 24 hours. Participants in the study received 32 ounces of drinks for each intervention. The energy drinks were similar in content, except for some differences in ingredients including carnitine, guarana, and Panax ginseng. The results of the study demonstrated that both energy drinks significantly prolong QTc interval and raise blood pressure. These effects were mostly seen within 4 hours post-consumption (Shah 2019).

Other researchers attempted to investigate specific ingredients on cardiovascular parameters. Fletcher and colleagues investigated effects of energy drink versus caffeinated control drink on QT prolongation and blood pressure elevation. The study demonstrated a significant difference of the baseline-adjusted QTc interval at 2 hours and peripheral blood pressure elevation at 6 hours (Fletcher 2017) between the energy drink and caffeinated control drink. The study

suggested that caffeine might not be the likely cause of QT prolongation and there might be other ingredients that might have caused the QT prolongation. Another randomized controlled trial comparing effects of energy drinks, Panax ginseng, and placebo on QTc prolongation showed significant difference of between energy drinks and placebo at 2 hours, while Panax ginseng alone did not contribute to QT prolongation effect (Shah 2016). Furthermore, a randomized controlled trial published early this year conducted a research to investigate the effects of control drinks containing caffeine, glucuronolactone, or taurine alone or in combination and compare them energy drinks containing the same amount of the ingredients above and placebo. Caffeine-containing drinks were shown to raise blood pressures while when taurine is added to caffeine-containing drinks, it was shown to shorten QTc interval and no significant difference was seen for systolic blood pressure. In addition, glucuronolactone-containing drinks resulted in shortened QTc interval when compared to placebo (Basrai 2019).

Most studies that have shown significant QT prolongation after energy drink consumption compared high-volume (32 ounces) energy drinks to placebo drinks (Fletcher 2017, Shah 2019). It is questionable if we can extrapolate the results obtained previously from high-volume energy drink studies to general public, given the largest volume of energy drinks currently available on the market is 24 ounces. Wiklund et al. investigated the use of 25 ounces energy drinks in their study participants and show no change in heart rhythm. The study arms include a group receiving energy drinks after overnight fasting and another group after 30 minutes of maximal exercise, a group receiving energy drinks with alcohol after 30 minutes of maximal exercise, and a control group receiving no drink after similar amount of exercise (Wiklund 2003). Because of the complexity of the study design and interventions, there are limitations to generalize the results in everyday life setting. Another study was conducted to compare 16 ounces energy

drinks, 24 ounces energy drinks, caffeine, and water. The authors found no difference in cardiovascular measurements, including QT interval. However, there are variabilities in the study interventions, such as variable volume of the fluids received by each study group or different caffeine content, that might affect their findings. In addition, the study was underpowered, which made it less likely for small changes in the measurements to be detected (Brothers 2017). Basrai and colleagues also conducted volume effects evaluation in their study comparing 750 milliliters (~25 ounces) and 1,000 milliliters (33 ounces) energy drinks, which they found to have no different on cardiovascular parameters in regard to different volumes, including QTc interval and blood pressure. However, the study did not report the comparison results of the lower-volume drink head to head with placebo after it was determined that both volumes did not have different effects on their outcomes (Basrai 2019). Given there is little known about the cardiovascular safety profile of 24 ounces energy drinks, further investigation will provide additional knowledge.

Objective and Hypothesis

The objective of this randomized, controlled, crossover, double-blind clinical trial is to compare the effect of 24-ounce energy drinks and placebo in regard to QT interval prolongation and BP elevation. We hypothesize that 24-ounce energy drink will lead to greater QTc interval and blood pressure when compared to placebo.

The overall purpose of the study is to gain more information regarding safety profile of energy drinks that are currently available in the market. The study results may be used to help regulatory bodies to support or refute call to action for energy drink regulation or labeling standards.

Chapter 2: Methods

Study Oversight

IRB approval. The study involved human subjects. Research conduct was approved by University of the Pacific (UOP) Institutional Review Board (IRB) with protocol number 19-03.

Informed consent. As part of the IRB protocol, a written informed consent document was also generated. The document provided information to study subjects regarding the purpose of the study, how the research would be conducted, eligibilities to participate in the study, procedures to be followed, rundown of study visit schedules, potential risks of the study, risk managements, compensation information, confidentiality statement, and contact information of primary study investigator.

Prior to subject enrollment, study investigators ensured subjects understand the expectations and risks associated with the study. Consent was obtained from subjects by obtaining signatures of study subject, primary investigator, and a witness and dating the document. A copy of the signed informed consent was provided to each study subject.

Risk management. Subjects were observed for any adverse event during the study and followed throughout the study period. Safeguards were placed in order to eliminate and minimize the risks when subjects experienced adverse events. In the event of minor adverse events, subjects were informed to notify principal investigators and were provided with resolution promptly when necessary. For serious adverse events, subjects were informed to immediately contact 9-1-1 or go to the closest emergency department.

All subjects were provided with the primary investigator contact information to contact to discuss any adverse event they might be experiencing while offsite.

Study Population

Recruitment. For subject recruitment, flyers and listserv emails were distributed around the University of the Pacific (UOP) and Stockton community. Locations include UOP campus, San Joaquin Delta College, and nearby food and beverage shops. The contact information of the primary investigator was provided on the flyers and listserv emails for interested participants.

Screening criteria. After study subjects were consented, they were screened for eligibilities to participate in the study. Healthy volunteers with no medical condition between the age of 18 and 40 were enrolled. Subjects were excluded if they have any risk factors for cardiovascular diseases, including heart rhythm other than normal sinus, history of arrhythmia, family history of premature sudden cardiac death before the age of 60, left ventricular hypertrophy, atherosclerosis, hypertension, palpitations, t-wave abnormalities, baseline QTc interval greater than 450 ms. Subjects with BP greater than 140/90 millimeter mercury (mmHg), presence of any known medical condition, or concurrent use of any medication or herbal supplements on daily basis were excluded as well. The use of oral contraceptives are permitted as long as subjects have been stable on it for 1 month. Other exclusion criteria include current smoker or recent smoking in the month prior to enrollment, pregnancy or currently breastfeeding, non-English speaker, refusal to sign informed consent form, and unwillingness to follow study protocol. Other baseline information collected during the screening include age, height, weight, ethnicity, typical use of energy drink and other caffeinated beverage, average daily amount of sleep, and average amount of physical activity.

Information to determine eligibility was collected during the subject interview. Electrocardiogram (ECG), BP, and BG measurements were obtained to rule out exclusion criteria mentioned above. A pregnancy test was also conducted using urine dip stick tests for all female subjects who are capable of being pregnant.

Eligibility for study participation was determined during the screening visit and followed by study visits schedules. The first study visit (Day 1) could be conducted immediately after the screening if subjects have met all the inclusion and exclusion criteria and study protocol requirements.

Study Design

Design. The study design is a randomized, controlled, double-blind, crossover clinical trial. Subjects were assigned randomly to two study arms. On 2 separate days, each subject consumed:

1. 24-ounces of energy drink (ingredients include 240 mg caffeine, 81 g sugar, 5.1 mg vitamin B2, 60 mg of vitamin B3, 6 mg of vitamin B6, 18 mcg of vitamin B12, 3000 mg of taurine, 600 mg of Panax ginseng, and 7,500 mg of proprietary energy blend including L-carnitine, glucose, caffeine, guarana, inositol, glucuronolactone, and maltodextrin)
2. 24-oz of cherry- and lime-flavored, carbonated placebo drink (ingredients include 30 mL lime juice, 105 mL of cherry syrup, and 575 mL of carbonated water)

Study products were bought from standard vendors and compounded prior to sessions. 24-ounces energy or placebo drinks were divided into two 12-ounces tinted bottles. Study investigators and subjects were blinded as to what interventions each subject received on each study day. All study drinks were made and packaged by unblinded member of the study team.

Study visit timeline. Prior to each study visit, all subjects were required to refrain from caffeine, alcohol, and energy drink consumption at least 48 hours and fast overnight with no food

or drinks except water 10 hours prior to each study visit. There were 2 scheduled visits with at least 6 days washout period between each visit for all subjects.

During each visit, baseline measurements of ECG and BP were obtained before subjects consumed the study drinks. Subjects were required to consume the drinks no faster than 15 minutes per bottle. The time clock for study duration started at the beginning of the drinking process. Repeated measurements of cardiovascular parameters were made at an hourly interval over 4 hours. In addition, assessment of any side effect experienced was also obtained hourly. All measurements were recorded on the subject data collection form. Subjects were asked to keep activity to minimal until last measurements were collected. Snacks were available for subjects when requested.

Measurements

Baseline characteristics. Demographic information were collected during the screening visit. History of regular caffeine or energy drink intake and sleeping pattern were also obtained from subject.

Electrocardiogram. Standard 12-lead ECG machines (Philips PageWriter Trim III and TC20, Philips Medical Systems, Andover, MA) were used to obtain QT interval, PR interval, and QRS duration. The QT interval obtained was further corrected to QTc with Bazett's equation (QTcB) by the ECG. QTc with Fridericia's equation (QTcF) was also calculated using the equation below.

$$\text{QTcF} = \frac{QT\ (in\ ms)}{\sqrt[3]{RR\ (in\ second)}}$$

ECG measurements were conducted at baseline (0 minute), 60 minutes, 120 minutes, 180 minutes, and 240 minutes with subjects in supine position on each study visit day. All electrocardiogram measurements were taken three times at each time point and averages were

calculated for data analysis. Calibration of the ECG machine was performed routinely to 1-milliVoltage/centimeter standardization with a paper speed of 25 millimeter/second.

SphygmoCor. Peripheral and central blood pressures were obtained using SphygmoCor (AtCor Medical Pty Ltd, West Ryde, Australia). Blood pressures were obtained at baseline (0 minute), 60 minutes, 120 minutes, 180 minutes, and 240 minutes with subjects in relaxed sitting position on each study visit day. Subjects were instructed to sit for 2 minutes after coming up from ECG measurements prior to SphygmoCor measurements. All blood pressure measurements were taken twice at each time point and averages were calculated for data analysis. In addition to blood pressures, SphygmoCor also measured heart rate and arterial stiffness, which was presented as augmentation index.

Adverse events. Subjects were observed and interviewed for any signs and symptoms of adverse events related to cardiovascular, gastrointestinal, and central nervous systems they might be experiencing during the study visits or anytime during the study period when they are offsite. Interview questions included presence of potential cardiovascular adverse events (tachycardia, elevated blood pressure, flushing sweating, or palpitations), gastrointestinal adverse events (nausea, vomiting, diarrhea, stomach upset, or loss of appetite), or central nervous system adverse events (agitation, hallucination, headache, insomnia, sleepiness, irritability, restlessness, dizziness, tingling sensation, or confusion). Subjects were also asked if they were experiencing other potential adverse effects including signs and symptoms not mentioned above.

Data Analysis

Endpoints. The primary endpoint of the study included the baseline-adjusted QTc (QTcB and QTcF) and peripheral systolic blood pressure (pSBP). Other endpoints that were collected included baseline-adjusted QT interval, PR interval, QRS duration, hear rate, peripheral diastolic

blood pressure (pDBP), central systolic and diastolic blood pressure (cSBP and cDBP), and augmentation index corrected at heart rate of 75 beats per minute(AI_{75}). Any occurrence and description of adverse events were also recorded. All endpoints were assessed at each measurement time points.

Power calculation. To achieve 80% power at an alpha level of 0.05 based on the primary endpoints of QTc and peripheral systolic BP, 18 subjects overall are needed to participate in the study. Assumptions were made for the endpoints to observe significant difference in QTc and central systolic blood pressures when comparing energy drink and placebo with anticipated of baseline-adjusted QTc of 10 ± 14 ms and systolic blood pressure of 4 ± 4 mmHg.

Statistical tests. Baseline characteristics and endpoints were reported using descriptive statistics; percentage for discrete variables and mean with standard deviation for continuous variables. Shapiro-Wilk test was used to determine normal distribution of the data given small sample size. Wilcoxon test was used to detect statistical difference for electrocardiogram and SphygmoCor endpoints while Chi-square test was used for adverse events. Both per protocol and intention to treat analyses were conducted for the baseline-adjusted maximum difference of endpoints between the energy drink and placebo arms. Mann-Whitney U test was used to determine any effect of randomization and duration of drinking on outcomes. Data collection and analysis were performed with Microsoft Excel (Version 16.10, Microsoft, Redmond, WA) and SPSS (Version 25, IBM Corporation, Armonk, New York).

Chapter 3: Results

Enrollment and Randomization

Twenty two subjects were screened for the study and 20 subjects met inclusion and exclusion criteria to be enrolled. Two subjects were excluded, one subject has a diagnosis of irritable bowel diseases and another subject's average QTc obtained during screening was greater than 450 ms. All enrolled subjects completed the study with no withdrawal.

Nine subjects (45%) received energy drinks on their first visit and then placebo drink in the second visit and 11 subjects (55%) vice versa. Most subjects on both visit days completed the drinks within 30 minutes. Five subjects (25%) completed the energy drinks and 3 subjects (15%) completed the placebo drinks after 30 minutes. All subjects completed the drinks within 60 minutes before the first measurement timepoint.

Baseline Characteristics

As presented in **Table 2**, subjects enrolled were 23 years old on average with even split in gender. Majority of the subjects (55%) were Asians, followed by Caucasian and few are African American and Hispanic. Most of the subjects (70%) rarely consumed energy drinks but most (75%) consumed other caffeinated beverage either occasionally or frequently. In terms of baseline cardiovascular parameters (refer to **Table 3**), all heart rhythm and blood pressure measurements were similar between the energy drinks and placebo arms ($p>0.05$).

Table 2: Baseline Characteristics

Characteristics	Total (n = 20)
Age (in year)	22.55 ± 5.37
Height (in inch)	66.90 ± 3.29
Weight (in pound)	160.14 ± 32.55
Sex (female)	10 (50)
Race	
Caucasian	5 (25)
African American	2 (10)
Asian	11 (55)
Hispanic	2 (10)
Energy drink consumption	
Rarely (<1 drink per month)	14 (70)
Occasionally (1-3 drinks per month)	3 (15)
Frequently (1-6 drinks per week)	2 (10)
Daily (1 or more drinks per day)	1 (5)
Non-energy drink caffeinated drink consumption	
Rarely (<1 drink per month)	3 (15)
Occasionally (1-3 drinks per month)	6 (30)
Frequently (1-6 drinks per week)	9 (45)
Daily (1 or more drinks per day)	2 (10)
Physical activity (in day per week)	3.78 ± 1.48
Amount of sleep (in hour per day)	6.26 ± 0.78

Data are reported in mean ± SD or n (%).

Table 3: Baseline Cardiovascular Parameters

	ED (n = 20)	PL (n = 20 for ECG and 19 for SphygmoCor)	P value
QTcB (ms)	423.27 ± 16.07	420.33 ± 18.94	0.247
QTcF (ms)	419.66 ± 14.84	419.31 ± 16.97	0.911
QT (ms)	413.63 ± 33.93	418.48 ± 33.29	0.952
PR (ms)	156.10 ± 20.11	154.00 ± 21.57	0.112
QRS (ms)	92.67 ± 8.88	93.22 ± 8.72	0.866
pSBP (mmHg)	117.93 ± 10.30	116.90 ± 11.00	0.420
pDBP (mmHg)	72.45 ± 6.18	71.74 ± 7.16	0.445
cSBP (mmHg)	104.40 ± 9.27	103.24 ± 10.29	0.227
cDBP (mmHg)	73.17 ± 6.03	72.64 ± 7.14	0.601
HR (bpm)	65.47 ± 11.68	65.23 ± 12.90	0.494
AI_{75}	5.07 ± 16.33	2.50 ± 17.82	0.227

All data are reported in mean ± SD. Abbreviation: AI_{75}, augmentation index corrected at heart rate of 75 beats per minute; bpm, beats per minute; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; ED, energy drink; HR, heart rate; mm Hg, millimeter mercury; ms, millisecond; pDBP, peripheral diastolic blood pressure; PL, placebo; PR, PR interval; pSBP,

peripheral systolic blood pressure; QRS, QRS duration; QT, QT interval; QTcB, corrected QT interval using Bazett's equation; QTcF, corrected QT interval using Fridericia's equation.

Cardiovascular Parameters

Normality. Normality test was conducted that shows ECG data from 20 subjects were not all normally distributed. It was then determined that nonparametric tests were needed to conduct data analysis.

Electrocardiogram. Baseline-adjusted ECG measurements at each timepoint are presented in **Table 4** and **Figure 1**. Baseline-adjusted QTcB and QTcF were found to be significantly greater in energy drink arm compared to placebo arm at hour 1, 2, and 3 and hour 4 for QTcF as well. In addition, baseline-adjusted QT interval was found to be significantly greater in energy drink arm at hour 1. Baseline-adjusted PR interval and QRS duration were similar between group at any timepoint.

Table 4: Baseline-Adjusted Electrocardiogram Measurements at Each Timepoint

		1 Hour	2 Hour	3 Hour	4 Hour
QTcB	**ED (n = 20)**	5.85 ± 11.66	1.77 ± 12.19	5.62 ± 15.10	3.38 ± 3.00
	PL (n = 20)	-1.35 ± 8.24	-6.27 ± 9.66	-4.00 ± 11.46	-1.08 ± 2.59
	Mean Difference	7.20 ± 9.27	8.03 ± 13.45	9.62 ± 12.51	4.47 ± 16.91
	P value	0.003*	0.014*	0.004*	0.502
QTcF	**ED (n = 20)**	2.69 ± 6.42	-1.27 ± 8.04	6.63 ± 11.76	6.61 ± 10.29
	PL (n = 20)	-3.47 ± 5.68	-7.37 ± 6.97	-1.80 ± 10.00	0.71 ± 10.07
	Mean Difference	6.16 ± 6.85	6.10 ± 8.82	8.43 ± 10.41	5.90 ± 10.07
	P value	0.002*	0.005*	0.001*	0.019*
QT	**ED (n = 20)**	-3.41 ± 14.33	-7.43 ± 17.54	8.43 ± 18.18	12.93 ± 25.68
	PL (n = 20)	-7.58 ± 15.55	-9.53 ± 14.67	2.72 ± 20.94	4.27 ± 20.89
	Mean Difference	4.18 ± 10.08	2.10 ± 15.10	5.72 ± 22.10	8.67 ± 25.07
	P value	0.019*	0.422	0.305	0.126
PR	**ED (n = 20)**	0.20 ± 6.26	-3.05 ± 5.71	-3.43 ± 6.53	-3.42 ± 7.82
	PL (n = 20)	2.70 ± 6.50	-2.13 ± 7.90	-3.75 ± 4.91	-5.75 ± 6.26
	Mean Difference	-2.50 ± 7.00	-0.92 ± 9.53	0.32 ± 8.33	2.33 ± 9.43
	P value	0.089	0.695	1.000	0.286
QRS	**ED (n = 20)**	2.78 ± 2.85	0.10 ± 2.34	0.73 ± 3.14	1.38 ± 3.54
	PL (n = 20)	3.93 ± 3.18	1.38 ± 2.84	0.42 ± 4.00	1.42 ± 4.05
	Mean Difference	-1.15 ± 3.00	-1.28 ± 2.73	0.32 ± 4.40	-0.03 ± 3.43
	P value	0.140	0.050	0.546	0.840

All data are reported in mean ± SD in millisecond unit. Abbreviation: ED, energy drink; ms, millisecond; PL, placebo; PR, PR interval; QRS, QRS duration; QT, QT interval; QTcB, corrected QT interval using Bazett's equation; QTcF, corrected QT interval using Fridericia's equation.

*P<0.05

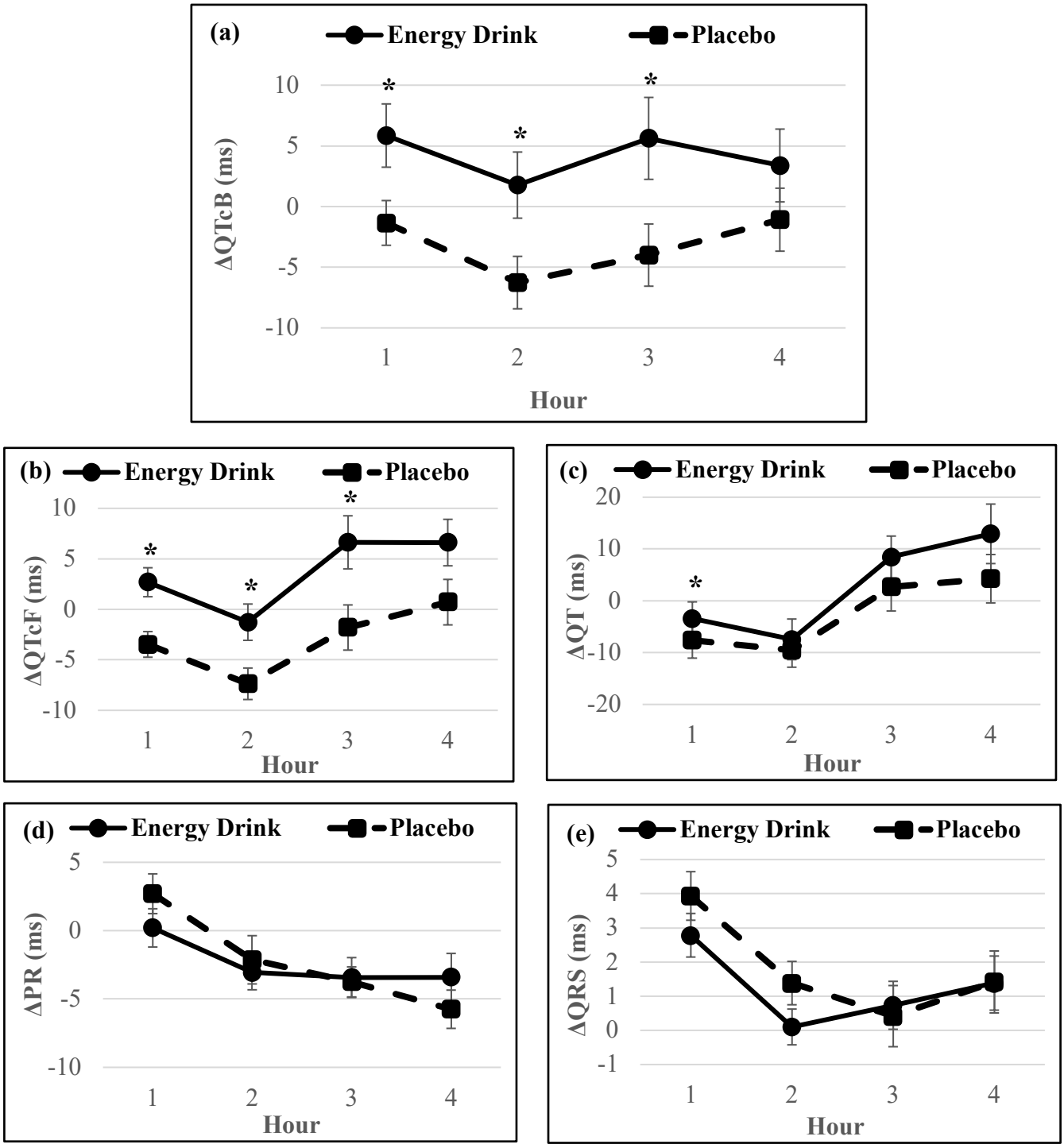

Figure 1: Baseline-adjusted electrocardiogram parameters at timepoints of 1, 2, 3, and 4 hours of **(a)** QTcB (corrected QT interval with Bazett's equation), **(b)** QTcF (corrected QT interval with Fridericia's equation), **(c)** QT (QT interval), **(d)** PR (PR interval), and **(e)** QRS (QRS duration).
Abbreviation: ms, millisecond.
*p <0.05 energy drink versus placebo comparison. Error bar depicts standard error of mean.

The maximum change from baseline in QTcB was significantly greater in energy drink arm compare to placebo with mean difference of 9.48 ± 13.84 ms (p = 0.007). Similarly, QTcF was found to be greater in energy drink arm (7.13 ± 10.55 ms, p = 0.006). QT interval, PR interval, and QRS duration were similar between arms (**Table 5**).

Per protocol analysis (**Table 6**) for ECG measurements was conducted due to incomplete data collection for one subject in the energy arm, specifically for the first measurement timepoint 1 hour post-consumption. Analysis demonstrated similar results as intention to treat analysis in terms of maximum change of QTcB and QTcF from baseline being significantly greater in energy drink arm and no difference was noted for PR interval, QT interval, and QRS duration. In addition, baseline-adjusted measurements at hour 1 show similar results when compared to intention-to-treat analysis where significant difference was observed for QTcB, QTcF, and QT interval, but no difference found for PR interval and QRS duration.

Two female and 1 male subjects had prolonged QTc within 4 hours after consuming energy drink at 493.67, 477.33, and 410.67 ms, respectively, with changes from baseline of over 30 ms. No subject was found with prolonged QTc interval in placebo arm, except for one female subject with prolonged QTc interval at baseline (474.33 ms) that is maintained throughout the study period with maximum QTc interval of 473 ms after consuming placebo drinks.

Table 5: Intention-To-Treat Average Maximum Change in Electrocardiogram Measurements

	ED (n = 20)	PL (n = 20)	Mean Difference	P value
QTcB	13.68 ± 12.71	4.20 ± 8.80	9.48 ± 13.84	0.007*
QTcF	10.59 ± 9.41	3.42 ± 8.41	7.17 ± 10.51	0.006*
QT	16.50 ± 21.93	7.25 ± 19.21	9.25 ± 23.87	0.135
PR	2.07 ± 6.36	4.57 ± 4.23	-2.50 ± 5.74	0.086
QRS	-6.47 ± 33.00	4.35 ± 2.87	-10.82 ± 34.23	0.513

All data are reported in mean ± SD and in millisecond unit. Abbreviation: ED, energy drink; ms, millisecond; PL, placebo; PR, PR interval; QRS, QRS duration; QT, QT interval; QTcB,

corrected QT interval using Bazett's equation; QTcF, corrected QT interval using Fridericia's equation.
*p<0.05

Table 6: Per-Protocol Analysis of Change in Electrocardiogram Measurements

		1 Hour (n = 19 for ED and n = 20 for PL)	Maximum (n = 20)
QTcB	**ED**	6.28 ± 11.81	13.68 ± 12.70
	PL	-1.04 ± 8.34	4.20 ± 8.80
	Mean Difference	7.32 ± 9.51	9.48 ± 13.84
	P value	0.005*	0.007*
QTcF	**ED**	2.51 ± 6.54	10.59 ± 9.41
	PL	-3.54 ± 5.82	3.42 ± 8.41
	Mean Difference	6.05 ± 7.02	7.17 ± 10.51
	P value	0.004*	0.006*
QT	**ED**	-4.63 ± 13.61	16.50 ± 21.93
	PL	-8.32 ± 15.62	7.25 ± 19.21
	Mean Difference	3.68 ± 10.11	9.25 ± 23.87
	P value	0.030*	0.135
PR	**ED**	-0.25± 6.10	2.07 ± 6.36
	PL	2.33 ± 6.47	4.57 ± 4.23
	Mean Difference	-2.58 ± 7.18	-2.50 ± 5.74
	P value	0.112	0.086
QRS	**ED**	2.40 ± 2.35	3.57 ± 3.15
	PL	3.70 ± 3.09	4.35 ± 2.87
	Mean Difference	-1.30 ± 3.01	-1.28 ± 2.73
	P value	0.083	0.108

All data are reported in mean ± SD and in millisecond unit. Abbreviation: ED, energy drink; ms, millisecond; PL, placebo; PR, PR interval; QRS, QRS duration; QT, QT interval; QTcB, corrected QT interval using Bazett's equation; QTcF, corrected QT interval using Fridericia's equation.
*p<0.05

SphygmoCor. Baseline-adjusted SphygmoCor measurements at each timepoint were presented in **Table 7** and **Figure 2**. Baseline-adjusted peripheral blood pressures and cDBP were

found to be significantly greater in energy drink arm compared to placebo arm at hour 1 and 2. Baseline-adjusted cSBP, HR, and AI_{75} were similar between group at any timepoint.

Table 7: Baseline-Adjusted SpygmoCor Measurements at Each Timepoint

		1 Hour	2 Hour	3 Hour	4 Hour
pSBP (mmHg)	**ED (n = 20)**	7.05 ± 6.36	5.80 ± 5.20	5.78 ± 6.34	6.63 ± 5.70
	PL (n = 20)	3.28 ± 7.34	0.95 ± 6.81	1.88 ± 7.15	3.35 ± 7.40
	Mean Difference	3.78 ± 6.74	4.85 ± 8.74	3.90 ± 10.08	3.28 ± 8.81
	P value	0.024*	0.027*	0.112	0.142
pDBP (mmHg)	**ED (n = 20)**	3.33 ± 4.74	4.13 ± 4.68	2.40 ± 5.34	3.78 ± 5.00
	PL (n = 20)	1.38 ± 4.10	0.13 ± 3.94	0.55 ± 4.14	1.70 ± 5.99
	Mean Difference	1.95 ± 4.33	4.00 ± 5.47	1.85 ± 6.10	2.08 ± 5.87
	P value	0.052	0.003*	0.286	0.163
cSBP (mmHg)	**ED (n = 20)**	4.20 ± 4.44	3.75 ± 5.26	3.16 ± 5.46	4.37 ± 5.29
	PL (n = 20)	1.07 ± 5.81	-6.91 ± 6.00	0.29 ± 5.93	1.72 ± 7.19
	Mean Difference	3.13 ± 6.17	4.44 ± 8.14	2.87 ± 9.09	2.65 ± 8.49
	P value	0.057	0.052	0.167	0.296
cDBP (mmHg)	**ED (n = 20)**	3.67 ± 4.63	4.63 ± 4.45	2.54 ± 5.25	4.03 ± 4.88
	PL (n = 20)	1.59 ± 4.17	0.40 ± 3.84	0.63 ± 4.56	1.83 ± 6.01
	Mean Difference	2.08 ± 4.17	4.24 ± 5.06	1.91 ± 6.46	2.20 ± 5.72
	P value	0.037*	0.001*	0.247	0.135
HR (bpm)	**ED (n = 20)**	4.47 ± 5.84	3.65 ± 6.77	-0.51 ± 8.45	-1.61 ± 9.20
	PL (n = 20)	3.40 ± 6.26	1.80 ± 5.97	-1.57 ± 6.11	-2.37 ± 6.03
	Mean Difference	1.07 ± 6.97	1.85 ± 9.37	1.06 ± 9.94	0.76 ± 10.92
	P value	0.351	0.313	0.575	0.765
AI_{75}	**ED (n = 20)**	-8.37 ± 5.76	-8.25 ± 8.41	-10.20 ± 6.71	-10.09 ± 9.38
	PL (n = 20)	-8.78 ± 7.58	-8.35 ± 10.39	-8.68 ± 10.64	-8.62 ± 14.85
	Mean Difference	0.41 ± 9.91	0.10 ± 12.57	-1.52 ± 13.45	-1.47 ± 16.86
	P value	0.737	0.970	0.627	0.970

All data are reported in mean ± SD. Abbreviation: AI_{75}, augmentation index corrected at heart rate of 75 beats per minute; bpm, beats per minute; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; ED, energy drink; HR, heart rate; mm Hg, millimeter mercury; pDBP, peripheral diastolic blood pressure; PL, placebo; pSBP, peripheral systolic blood pressure.
*$p<0.05$

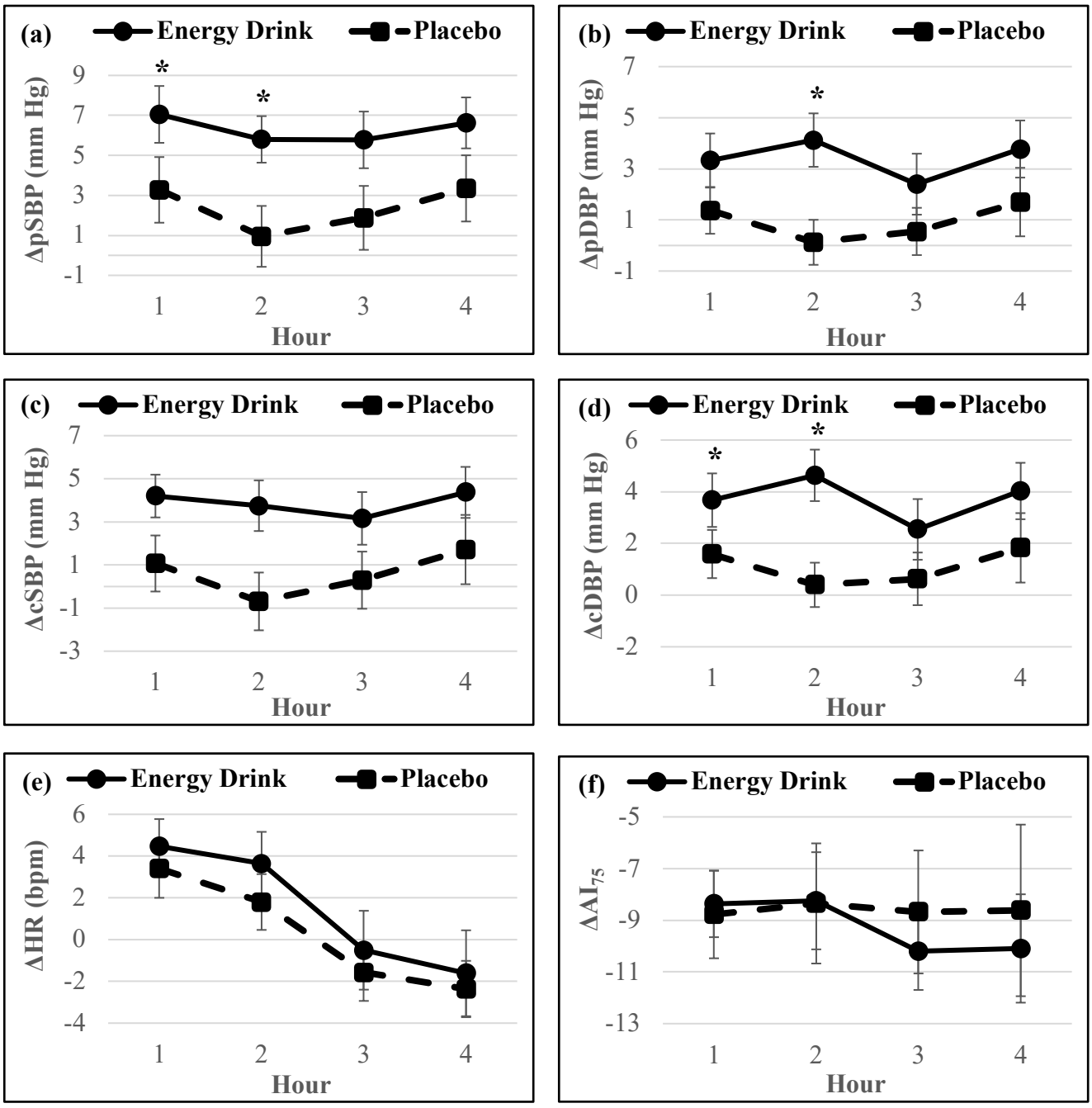

Figure 2**:** Baseline-adjusted SphygmoCor parameters at timepoints of 1, 2, 3, and 4 hours of **(a)** pSBP (peripheral systolic blood pressure), **(b)** pDBP (peripheral diastolic blood pressure), **(c)** cSBP (central systolic blood pressure), **(d)** cDBP (central diastolic blood pressure), **(e)** HR (heart rate), and **(f)** AI_{75} (augmentation index corrected at heart rate of 75 beats per minute).
Abbreviation: bpm, beats per minute; mm Hg, millimeter mercury.
*p <0.05 for energy drink versus placebo comparison. Error bar depicts standard error of mean.

The maximum change from baseline in pSBP was significantly greater in energy drink arm compare to placebo with mean difference of 5.03 ± 9.38 mmHg (p = 0.006). Similarly, pDBP, cSBP, and cDBP were found to be greater in energy drink arm. HR and AI_{75} were similar between arms (**Table 8**).

Per protocol analysis (**Table 9**) for SphygmoCor measurement was also conducted due to incomplete data collection for one subject. Analysis demonstrated similar results as intention to treat analysis in terms of maximum change of all blood pressures from baseline being significantly greater in energy drink arm and no difference was noted for HR and AI_{75}.

Three subjects had peripheral blood pressure of greater than 140/90 mmHg within 4 hours after consuming energy drinks at 145/92, 154/92, and 145/93 mmHg, while 9 subjects with greater than 130/80 mmHg. Changes from baseline of pSBP ranged between 8 and 23 mmHg while changes from baseline of pDBP ranged between 13 and 15 mmHg for those reaching more than 140/90 mmHg. None of the subjects in placebo arms had peripheral blood pressure greater than 140/90 mmHg, while 3 subjects had pSBP greater than 130 mmHg and 3 subjects had pDBP greater than 80 mmHg.

Table 8: Intention-To-Treat Average Maximum Change in SphygmoCor Measurements

	ED (n = 20)	PL (n = 20)	Mean Difference	P value
pSBP (mmHg)	11.10 ± 5.24	6.08 ± 7.07	5.03 ± 9.38	0.006*
pDBP (mmHg)	6.88 ± 4.61	3.93 ± 4.55	2.95 ± 6.02	0.033*
cSBP (mmHg)	7.96 ± 5.08	3.79 ± 6.36	4.17 ± 9.08	0.037*
cDBP (mmHg)	7.16 ± 4.48	4.24 ± 4.50	2.92 ± 5.86	0.021*
HR (bpm)	7.02 ± 5.18	5.33 ± 6.65	1.70 ± 7.91	0.279
AI_{75}	-4.06 ± 6.76	-3.36 ± 11.78	-0.70 ± 12.76	0.823

All data are reported in mean ± SD. Abbreviation: AI_{75}, augmentation index corrected at heart rate of 75 beats per minute; bpm, beats per minute; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; ED, energy drink; HR, heart rate; mmHg, millimeter mercury; pDBP, peripheral diastolic blood pressure; PL, placebo; pSBP, peripheral systolic blood pressure.

*p<0.05

Table 9: Per-Protocol Average Maximum Change in SphycomoCor Measurements

	ED (n = 19)	PL (n = 19)	Mean Difference	P value
pSBP (mmHg)	11.05 ± 5.38	5.76 ± 7.12	5.29 ± 9.56	0.006*
pDBP (mmHg)	6.45 ± 4.31	3.34 ± 3.83	3.11 ± 6.14	0.033*
cSBP (mmHg)	7.93 ± 5.22	3.32 ± 6.17	4.61 ± 9.10	0.020*
cDBP (mmHg)	6.75 ± 4.20	3.66 ± 3.79	3.09 ± 5.97	0.020*
HR (bpm)	6.84 ± 5.25	5.17 ± 6.79	1.67 ± 8.12	0.334
AI_{75}	-4.14 ± 6.93	-3.76 ± 11.96	-0.38 ± 13.03	0.687

All data are reported in mean ± SD. Abbreviation: AI_{75}, augmentation index corrected at heart rate of 75 beats per minute; bpm, beats per minute; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; ED, energy drink; HR, heart rate; mmHg, millimeter mercury; pDBP, peripheral diastolic blood pressure; PL, placebo; pSBP, peripheral systolic blood pressure.
*p<0.05

Effects of randomization and drinking duration. No difference of average maximum change in ECG and SphygmoCor measurements was found between the group who received energy drinks and those received placebo drink first (p>0.05 for all endpoints when compared between groups). Similarly, no difference was observed on all average maximum change in ECG and SphygmoCor measurements between group that complete energy drink within 30 minutes versus those that complete the drinks longer than 30 minutes (p>0.05 for all endpoints when compared between groups).

Adverse Events

Overall, significant proportions of subjects receiving energy drinks reported adverse events compared to those receiving placebo drinks (90% vs. 30%, p<0.001). More subjects receiving energy drinks experienced cardiovascular and central nervous system adverse events as shown in **Table 10**. Most notable cardiovascular adverse events being reported were faster heartbeat,

while report for central nervous system adverse events include lightheadedness and restlessness after energy drink consumption. More subjects receiving energy drinks were also complaining on experiencing nausea. All adverse events were reported during the study visits, except for one subject who reported vomiting at the night of study visit after receiving placebo drink. None of the adverse events resulted in discontinuation of any study participant.

A number of subjects reported feeling hungry due to overnight fasting and snacks were provided upon requests. Five subjects in each energy drink and placebo arm were provided with snacks that include Nature Valley granola bar and/or Orchard Valley Harvest trail mix. One subject brought own snacks including banana and madeline that were verified and approved to be consumed during study visit by research investigator. One subject was accidentally provided with Quaker granola bar that contained chocolate chip on first study visit day. Given chocolate chip contains caffeine and may interfere with study results, subject was provided with similar granola bar around the same timing on the second visit day.

Table 10: Adverse Event Reports

Adverse Events	ED (n = 20)	PL (n = 20)	P value
Cardiovascular	11 (55%)	1 (5%)	0.001*
Faster heartbeat	9 (45%)	1 (5%)	0.003*
Sweating	1 (5%)	0 (0%)	0.311
Palpitation	1 (5%)	0 (0%)	0.311
Central Nervous System	13 (65%)	5 (25%)	0.011*
Agitation	2 (10%)	0 (0%)	0.147
Headache	1 (5%)	1 (5%)	1.000
Lightheadedness	4 (20%)	0 (0%)	0.035*
Restlessness	9 (45%)	1 (5%)	0.003*
Tremor	2 (10%)	0 (0%)	0.147
Lethargy	0 (0%)	3 (15%)	0.072
Gastrointestinal	7 (35%)	3 (15%)	0.144
Bloating	1 (5%)	1 (5%)	1.000
Nausea	4 (20%)	0 (0%)	0.035*
Vomiting	0 (0%)	1 (5%)	0.311
Loss of appetite	1 (5%)	0 (0%)	0.311
Upset Stomach	0 (0%)	1 (5%)	0.311
Others	5 (25%)	2 (10%)	0.212
More frequent urination	3 (15%)	2 (10%)	0.633
Heavier breathing	2 (10%)	0 (0%)	0.147

All data are reported in n (%). Abbreviation: ED, energy drink; PL, placebo.
*$p<0.05$

Chapter 4: Discussion

Study Impact

The present study investigated the cardiovascular effects of low volume energy drinks on healthy individuals in a controlled setting. By far, most studies that show association of energy drinks with concerning cardiovascular effects investigated higher volume energy drinks, typically 32 ounces. Our study show that even lower-volume, 24-ounces energy drink may be capable of prolonging QTc interval and raising blood pressure significantly.

The results of this study are comparable to those from trials investigating high volume energy drinks. In a randomized controlled trial that enrolled 34 subjects and measured cardiovascular parameters for 4 hours post-consumption, 2 different energy drinks were shown to prolonged QTc interval when compared to placebo by 6 to 7.6 ms ($p = 0.005$). In the same study, blood pressures, including pSBP, pDBP, cSBP, and cDBP, were also significantly greater after energy drink consumption when compared to placebo ($p<0.001$). pSBP was found to be greater in energy drink arm by 4.6 to 6.1 mmHg. It was noted that when compared to placebo, changes from baseline in QTc interval were specifically greater at 3, 3.5, and 4 hours while changes in pSBP were significant at all measurement timepoints post-consumption (Shah 2019). Another trial comparing energy drink, Panax ginseng, and placebo also demonstrated significant prolongation of QTc interval by 6.56 ms and elevation of pSBP by 4.67 mmHg ($p<0.033$), specifically 2 hours after consuming energy drink when compared to placebo (Shah 2016). Basrai and colleagues found that 1,000 mL (~33 ounces) energy drink significantly raised peripheral blood pressures and heart rate ($p<0.05$) 1 hours post-consumption when compared to control drink, while no difference was observed for QTc interval. However, the study only measured endpoints 1, 3, 7, and 11 hours after consumption, thus effects of drinks between hour

1 and 3 were not captured in the study (Basrai 2019). Our study demonstrated similar results where maximum changes from baseline of QTc and blood pressures were significantly greater in energy drink arm than placebo arm, but no difference in heart rate was observed. In our study population, prolonging QTc interval was specifically observed in the first 3 hours post-consumption, while elevation of peripheral blood pressures in the first 2 hours post-consumption.

In contrast to few studies investigating lower volume energy drinks, our study demonstrated significant effect of energy drink on cardiovascular parameters. A study comparing 16 and 24 ounces energy drinks, caffeinated drink, and water as placebo demonstrated that energy drinks at either volume did not significantly affect blood pressure or QTc interval when compared to either caffeinated drink or water (Brothers 2017). Other study with even lower size of energy drinks of 500 mL (~16 ounces) show no significant effect on cardiovascular parameters. A randomized controlled trial, enrolling 24 subjects with familial long QT syndrome, found significantly higher peripheral blood pressures in energy drink arm compared to control drink with an increase of 6 mmHg ($p = 0.046$) but no significant change in primary endpoint of QTc interval (Gray 2017). Steinke and colleagues found a significant changes of blood pressure, heart rate, and QTc interval from baseline in a study evaluating the effect of 500 mL (~16 ounces) energy drinks over 4 hours post-consumption. The study, however, did not include a placebo arm. Other than volume difference, the study also noted different amount of taurine and caffeine in their energy drink versus ours (Steinke 2009). Given lack of evidence regarding the effect of each energy drink ingredient on cardiovascular parameters, it is possible that different amount of the ingredients might affect study outcomes.

This study might be the only randomized controlled study that specifically investigate 24 ounces energy drink and demonstrated negative impact of energy drink on both QTc interval and blood pressures. The results add confirmation to safety concerns associated with energy drinks and thus, warrants the need to increase awareness on risk associated with regular consumption. Even though prolongation QTc interval is not a fatal condition, it is a big risk factor for development for life-threatening arrhythmia, especially for high-risk individuals. Many QT-prolonging medications that induce QTc prolongation of at least 6 ms carry black box warnings or were removed from the market by FDA (Avelox1999, Li 2017). Given these facts, it is concerning to observe that 24-ounces energy drink consumptions in our study were able to induce over an average of 7 ms QTc prolongation when they are not regulated and available to be freely purchased by general public.

Furthermore, energy drinks impact on blood pressure cannot be ignored either. Although the changes from baseline were small, but small changes can make a big difference considering recent update in hypertension guideline with stricter blood pressure cutoff for diagnosis of hypertension (Whelton 2018). In our study, almost half of our study participants would fall above the blood pressure cutoff for hypertension diagnosis of greater than 130/80 after consuming energy drinks. Even though it was noted that increase in blood pressures were only maintained for approximately 2 hours after energy drink consumption, the effect of regular or chronic consumption of energy drinks to blood pressures is still unknown.

Study Limitations

Though our study evaluated the largest can of energy drinks available in the market, consuming 24 ounces of energy drinks at once may not be the typical consumption pattern in the general population. Most accessible marketplace, such as convenience or grocery stores, usually

carry even lower volume of energy drinks in 8 or 16 ounces. In addition, our study only evaluated one brand of energy drink while there are many that are commercially available that might contain different ingredients with different amount. There were not many studies available that investigate each ingredient in energy drinks and there is controversy regarding the effects of some ingredients on cardiovascular parameters (Basrai 2019, Fletcher 2017, Shah 2016). Therefore, there were still safety concerns regarding the ingredients used in energy drinks.

Our study population might not be the best representative of US population given majority of participants were Asians. Additionally, only as small number of our study participants reported consuming energy drinks regularly. It is questionable if regular energy drink consumers would experience similar effects from energy drinks and it is unknown if chronic consumption of energy drinks would have affected acute changes of cardiovascular parameters. Given our study had a set of inclusion and exclusion criteria, all of the participants were considered healthy with no concurrent medications taken. Our study results may not be applicable for those who might have comorbidities or taking medical products that might have possible interactions with energy drink or its ingredients.

A limitation of the study protocol is that there is no maximum time allowed for subjects to complete their drinks. Therefore, some participants have varying amount of time they took to complete the drinks. This might affect energy drink distribution and the timing of its cardiovascular effects. However, subgroup analysis was performed that shows the duration for completing energy drinks did not affect cardiovascular parameters. It was also observed that some participants, who were familiar with energy drink taste, were able to notice the drinks they received and possible self-unblinded during the study period.

Conclusion

This study suggested that lower volume (24 ounce) energy drinks may have acute effects on prolonging QTc interval and raising blood pressures after consumption. Given the results of our study, regular energy drink consumers and high-risk individuals to serious cardiovascular events should be aware of the risk of consumption. Further investigations are warranted, especially to evaluate the ingredients in energy drinks and chronic consumption of energy drinks.

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