Effects of Chronic Energy Drink Consumption on Cardiometabolic Endpoints

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EFFECTS OF CHRONIC ENERGY DRINK CONSUMPTION ON CARDIOMETABOLIC ENDPOINTS

by

May Chen

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Stockton, California

2019
EFFECTS OF CHRONIC ENERGY DRINK CONSUMPTION ON CARDIOMETABOLIC ENDPOINTS

By

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Effects of Chronic Energy Drink Consumption on Cardiometabolic Endpoints

Abstract

By May Chen
University of the Pacific
2019

Background: Since its introduction in the early 2000s, energy drinks have become increasingly popular among an extensive range of consumers, including adolescents and young adults. Currently, the United States Food and Drug Administration (FDA) does not regulate the formulation of energy drinks, which may vary widely in the amounts of caffeine and sugar, as well as various types of supplements. Recent reports of severe and fatal adverse effects related to energy drinks have led to growing concerns on the safety of energy drink consumption.

Objective: This study aimed to investigate the effects of chronic daily consumption of energy drinks on cardiometabolic endpoints, including blood pressure, ECG parameters, blood glucose, lipid parameters, weight, body mass index, and body fat consumption in a healthy adult population.

Methods: The study was an unblinded, non-randomized, proof-of-concept, prospective study that evaluated the effects of chronic consumption of energy drinks in a healthy, adult population. Each participant consumed two 16 oz. cans of a commercially available ED daily in two divided doses for 28 days. Investigators met with the participants on days 0, 7, 14, 21, and 28 of the study. Participants were required to complete a standardized log of consumption, which include date and time of consumption, as well an estimate of additional caffeine intake. The following measurements were taken for each participant over the 28 days: blood pressure (BP), electrocardiogram (ECG), fasting blood glucose (FBG), fasting lipid panel (FLP), weight, BMI, body fat composition, and serum creatinine. Adverse side effects related to energy drink
consumption were also recorded. Wilcoxon signed-rank tests were used to compare and detect statistical difference between endpoints for baseline and maximum post-dose systolic BP, QTc, FBG, FLP, weight, BMI, body fat, and serum creatinine values.

Results: Of the 14 total participants that were enrolled in the study, 12 participants completed the full study protocol for 28 days. Maximum measurements in peripheral systolic blood pressure (pSBP), peripheral diastolic blood pressure (pDBP), central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), and heart rate (HR) were found to be statistically significantly higher than baseline measurements (all P < 0.05). The maximum change from baseline to maximum pSBP, pDBP, cSBP, and cDBP were 9±7 mmHg, 5±4 mmHg, 7±6 mmHg, 5±4 mmHg, respectively. Maximum QTcB and QTcF intervals were also statistically higher than baseline (both P = 0.001). The maximum change from baseline in QTcB and QTcF interval were 19±13 ms and 15±10 ms, respectively. Both QTcB and QTcF intervals on days 7, 14, 21, and 28 were all found to be significantly higher than baseline (all P<0.05). There was a statistically significant increase in maximum FBG from baseline with an average increase 4±9 mg/dL (P=0.048). There were no detectable significant differences found between the various body composition analysis endpoints, including weight, BMI, percentage of body fat, fat mass, muscle mass, bone mass, and visceral fat rating. There was also no difference between baseline and day 28 in FLP and serum creatinine. The most common reported adverse side effects related to energy drink consumption include jitteriness, feeling energized and alert, fatigue, energy crash, and upset stomach.

Conclusion: Due to the increasing popularity of energy drinks and related serious adverse events, it is important to study the health impact of ED consumption. This study demonstrated that chronic energy drink consumption can lead to significant sustained elevations in blood pressure and heart rate, as well as increases in QTc interval and fasting blood glucose. Further research is necessary to understand the potential long-term consequences of energy drinks on chronic health conditions.
# TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CHAPTER

1. Introduction

2. Review of Literature
   - Energy Drink Consumption Patterns
   - Reported Adverse Events Associated with Energy Drinks
   - Current Literature on the Effects of Energy Drinks on Cardiovascular Parameters
   - Current Epidemiology of Diabetes, Hypertension, and Obesity
   - Objective and Purpose
   - Hypothesis

3. Materials and Methods
   - Study Oversight
   - Study Population
   - Study Design and Interventions
   - Study Measurements
   - Data Analysis

4. Results
   - Study Population
   - Cardiovascular Endpoints
   - Metabolic Endpoints
LIST OF TABLES

Table

1. Baseline characteristics of study participants............................................................... 27
2. Intention-to-treat maximum change in SphygmoCor PWA endpoints......................... 29
3. Per-protocol maximum change in SphygmoCor PWA endpoints................................ 29
4. Intention-to-treat maximum change in electrocardiogram endpoints.......................... 31
5. Mean QTc intervals during study period........................................................................ 32
6. Per-protocol maximum change in electrocardiogram endpoints.................................. 32
7. Intention-to-treat maximum change in blood glucose and body composition analysis... 35
8. Per-protocol comparison of baseline vs. day 28 of FLP and serum creatinine............ 35
9. Reported adverse effects during study period............................................................... 37
LIST OF FIGURES

Figure

1. Participants who were enrolled and included in data analysis........................................27
2. Mean SphygmoCor® endpoints by study day.................................................................30
3. Mean electrocardiogram endpoints by day.................................................................33
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aix@75</td>
<td>Augmentation index corrected at heart rate of 75 bpm</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>bpm</td>
<td>Beats per minute</td>
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<tr>
<td>cDBP</td>
<td>Central diastolic blood pressure</td>
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<tr>
<td>cSBP</td>
<td>Central systolic blood pressure</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>ED</td>
<td>Energy drinks</td>
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<tr>
<td>FBG</td>
<td>Fasting blood glucose</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FLP</td>
<td>Fasting lipid panel</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>ms</td>
<td>Millisecond</td>
</tr>
<tr>
<td>pDBP</td>
<td>Peripheral diastolic blood pressure</td>
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<tr>
<td>pSBP</td>
<td>Peripheral systolic blood pressure</td>
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<tr>
<td>QTc</td>
<td>Corrected QT interval</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>TC</td>
<td>Total cholesterol</td>
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<td>TG</td>
<td>Triglycerides</td>
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Chapter 1: Introduction

The popularity of energy drinks (EDs) has increased over the last few decades with marketing promoting their use as mental and physical performance enhancers (Heckman, Sherry, & De Mejia, 2010). While caffeine is a major ingredient in most EDs (ranging from 80 mg to 500 mg per drink), they may also contain various supplements, such as guarana, taurine, ginseng, B vitamins, gluconolactone, yohimbe, carnitine, and bitter orange, as well as a high amount of sugar (ranging from 25-50 grams per ED) (National Center for Complementary and Integrative Health, (NCCIH), 2017). The United States (US) Food and Drug Administration (FDA) currently regulates the maximum caffeine content in a 12-oz. serving of cola soda at 71 mg, though there are currently no regulations on the caffeine content in EDs. The FDA has also recommended that a daily intake of 400 mg caffeine (approximately 4-5 cups of coffee) in adults is generally safe and not associated with dangerous, negative effects (NCCIH, 2017; Rosenfeld, Mihalov, Carlson, & Mattia, 2014). The Substance Abuse and Mental Health Services Administration (SAMHSA) reported a doubling of emergency department visits involving adverse reactions due to EDs from 10,068 visits in 2007 to 20,783 visits in 2011 (2013). Commonly reported adverse reactions include insomnia, nervousness, headache, tachycardia, and seizures. ED consumption has also been linked with several deaths caused by cardiac arrest and life-threatening arrythmias.

As the use of energy drinks, particularly regular consumption, increases, the health impact of chronic use remains unknown. Several reviews have demonstrated ingestion of sugar-sweetened ED to significantly increase cardiac workload through increase of blood pressure and heart rate (Grasser et al., 2016; Wassef, Kohansieh, & Makaryus, 2017). In addition to case reports linking ED consumption with life-threatening events, consumption of large volume of energy drinks has been shown to acutely increase corrected QT (QTc) interval and systolic blood pressure (BP) when compared with caffeine alone, which demonstrates an increased risk of life-
threatening arrhythmias (Fletcher et al., 2017; Mangi, Rehman, Rafique, & Illovsy, 2017). While current literature has focused on acute effects, there are no studies that investigate the effect of chronic consumption of energy drinks, specifically the possible changes in hemodynamic, ECG, and glycemic parameters.
Chapter 2: Review of Literature

Energy Drink Consumption Patterns

As EDs become more popular, there is a growing use among adolescents and young adults. A survey of ED consumption patterns among 496 college students in the US showed that 51% of participants reported consuming greater than one ED each month (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007). The survey included 19 questions that addressed the types of EDs consumed, the side effects associated with ED use, and six common situations for energy drink use. Majority of energy drink users reported using EDs for insufficient sleep (67%), to increase energy (65%), and to drink with alcohol at parties (54%). For those that reported mixing EDs with alcohol, 49% consumed three or more energy drinks while partying.

Several studies have demonstrated the increasing popularity of energy drinks in adolescents. A survey of 2,629 Polish junior and senior high school students (aged 12-20 years; average age 15.8 years) showed that 66.8% of students consumed energy drinks, with 8% of drinkers consuming energy drinks several times per week and 6% of drinkers consuming energy drinks at least once a week (Nowak & Jasionowski, 2015). Males (p<0.01), students that played sports, and younger students (p=0.017) were more likely to consume EDs. About 24% of respondents reported mixing ED with alcohol, and age correlated significantly with this behavior as more senior high school students mixed ED with alcohol than junior high school students (p<0.01).

Similarly, a survey of 2,040 youth and young adults in Canada (aged 12-24; average age 18.3 years) revealed that 73.6% of respondents has consumed EDs, with 16% reported to consume more than 2 EDs in a day (Reid et al., 2017). ED products in Canada are required to report caffeine content in each container, as well as cautionary statements, such as “Do not consume more than (X) container(s)/serving(s) daily,” where (X) is 1 or 2, depending on the
product’s contents. There is also regulation that sets a maximum of 180 mg of caffeine per single-serving container. Of those that exceeded the maximum usage guidelines, older respondents (aged 18-19 and aged 20-24) had higher odds of consuming more than 2 EDs per day (odds ratio [OR] 2.07, 95% CI 1.08-3.97; OR 3.84, 95% CI 2.22-6.62, respectively).

The 2010 National Health Interview Survey data for 25,492 US adults estimated that 31.3% of adults were sports and energy drink consumers during the past 7 days, 21.5% of adults consumed 1 or more times per week, and 11.5% consumed 3 or more times per week (Park, Onufrak, Blanck, & Sherry, 2013). Characteristics of consumers that had significantly higher odds for drinking sports and EDs one or more times per week include adults with higher family income, those who lived in the South or West, adults who engaged in leisure-time physical activity, current smokers, and individuals with excellent satisfaction with their social activities and relationships. Age was most strongly associated with weekly consumption (OR 10.7 for ages 18-24, OR 6.4 for ages 25-39, OR 3.17 for ages 40-59 vs. age 60 or older). Consumption of sports drinks and EDs at least once a week was also positively associated with higher consumption of regular soda, coffee or tea drinks with added sugars, fruit drinks, milk, 100% fruit juice, and alcohol, indicating that consumers have tendencies to drink other sweet or caffeinated beverages and may perceive sports and EDs as healthy options.

**Reported Adverse Events Associated with Energy Drinks**

From 2007 to 2011, the number of emergency department visits involving EDs doubled from 10,068 visits to 20,783 visits (SAMSHA, 2013). In 2011, 58% of ED-related emergency room visits involved EDs only, while 42% involved other drugs, such as central nervous system stimulants. About 13% of visits involved EDs and alcohol and 10% involved EDs and illicit drugs. Consistently over the years, there were more male patients than females. While there were more patients aged 18-39 years than other age groups involved in ED-related visits each year from 2007 to 2011, the greatest increase in visits were observed among patients aged 40 years and older (279% increase). Common reported adverse events involving Red Bull®, 5-Hour
Energy®, and Monster® EDs include insomnia, nervousness/anxiety, headache, chest pain, tachycardia, seizures, nausea/vomiting, and fatigue (Center for Food Safety and Applied Nutrition, (CFSAN), 2015). Surveys of ED consumers reported episodes of “jolt and crash,” referring to having the feeling of a surge of energy, followed by a period of extreme fatigue (Malinauskas et al., 2007; Nowak & Jasionowski, 2015).

**Reported life-threatening effects related with EDs.** There are also numerous case reports linking life-threatening and fatal reactions to ED consumption. Many of the case reports involve cardiovascular changes after ED use, including supraventricular and ventricular arrhythmias, prolonged QT interval, myocardial infarction, coronary thrombosis, cardiomyopathy and aortic dissection (Goldfarb, Tellier, & Thanassoulis, 2014; Mangi et al., 2017). In 2001, a case report described the death of a 25-year-old female with a pre-existing mitral valve prolapse who had developed ventricular fibrillation after consuming Race 2005 Energy Blast with Guarana and Ginseng®, which contained approximately 660 mg of caffeine per 55 mL bottle (Cannon, Cooke, & McCarthy, 2001). Though the patient was previously evaluated by a cardiologist for her palpitations secondary to the mitral valve prolapse, her ECG was normal with no evidence of QTc prolongation. After consuming a 55 mL bottle of Race 2005 Energy Blast®, the patient collapsed at work and found to be in ventricular fibrillation, refractory to multiple defibrillation attempts. Since the death of this patient, Race 2005 Energy Blast® has been removed and recalled from the market.

Another case report described the death of a 28-year-old male with no significant past medical history or medication use who had collapsed during a basketball match after consuming 3 cans of EDs (Avcı, Sarıkaya, & Büyükcam, 2013). The patient reported to regularly consume the same 250-mL ED containing 80 mg of caffeine per can, at least 1 can per day for 7 months. He had no history of chronic conditions, smoking, illicit drug use, or anabolic steroid use, nor a family history of early death or coronary artery disease. The patient reported nausea and palpitation after drinking 3 EDs 5 hours before the basketball match and lost consciousness.
about 30 minutes into the match. Upon presentation, he was found to be in ventricular tachycardia, for which he received direct electric cardioversion and returned to normal sinus rhythm. While hospitalized, the patient had no further ECG changes, but died after sudden cardiac arrest on the third day.

In addition to life-threatening arrhythmias, other cardiovascular complications have been linked to ED use. A 54-year-old male with history of uncontrolled hypertension and obesity was admitted for chest pain and found to have an aortic dissection, requiring urgent reconstructive surgery (Jonjev & Bala, 2013). Patient reported consuming 4-5 EDs per night (mostly Red Bull®) to help him stay awake while driving as a professional truck driver. Upon hospital admission, the patient was found to be hypertensive (BP 190/110 mmHg) and tachycardic.

Despite numerous case reports of adverse effects related to EDs, there continues to be little regulation in the United States regarding its safety. However, recently, the American College of Sports Medicine (ACSM) has released new recommendations on the use of energy drinks, focusing on protecting children at risk of complications from energy drink consumption, advocating to stop marketing to at-risk groups, recommending avoidance of energy drinks before/during/after strenuous exercise, and calling for more education and research on the effects of energy drinks (Higgins, J. P., Babu, Deuster, & Shearer, 2018).

**Current Literature on the Effects of Energy Drinks on Cardiovascular Parameters**

While caffeine is the main active ingredient in EDs, it remains unclear if caffeine is the culprit in causing various adverse events associated with ED consumption. Literature demonstrates that chronic coffee consumption at 2-3 cups per day (~200-300 mg of caffeine) to be safe and is associated with neutral to beneficial effects for most of the studied health outcomes. This includes a possible reduction in risk of developing type 2 diabetes mellitus and hypertension, as well as certain cancers, neurological conditions, and liver conditions (Poole et al., 2017). Additionally, chronic coffee consumption is not associated with increased risk of
cardiac arrhythmias, coronary heart disease, or strokes (O’Keefe et al., 2013). However, high consumption of caffeine was demonstrated to have negative effects in pregnant women, leading to increased risk of preterm birth, low birth weight, and pregnancy loss (Poole et al., 2017).

On the other hand, when comparing ED consumption to drinking the same amount of caffeine, there is evidence of significant difference in cardiovascular response with ED consumption. In a meta-analysis investigating the impact of acute ED consumption on BP parameters, both systolic and diastolic BP were increased significantly by 4.44 mm Hg (95% CI = 2.71 to 6.17; Cochrane Q P = 0.001) and 2.73 mm Hg (95% CI = 1.52 to 3.95; Cochrane Q P = 0.050), respectively. Heart rate did not demonstrate a significant change (Shah, S. A. et al., 2016). The average caffeine content in the included studies was approximately 180 mg per ED dose. The meta-analysis also noted a possible dose-related effect between systolic BP elevation and caffeine dose. Caffeine consumption of less than 200 mg resulted in BP elevation of under 4 mmHg, compared to more than 6 mmHg of BP elevation with caffeine consumption more than 200 mg.

There is also evidence to show that there may be a difference between the degree of BP elevation caused by EDs vs. caffeine alone. When comparing head-to-head the effects of ED to caffeine supplementation of 24-hours ambulatory BP, mean 24-hour systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were significantly higher with ED than with caffeine supplementation (Franks, Schmidt, McCain, & Fraer, 2012). Additionally, daytime DBP and nighttime SBP and DBP were significantly higher in the ED group than the caffeine group, with a trend in higher daytime SBP and MAP noted. In a randomized, double-blind, controlled, crossover study investigating high-volume ED vs. caffeine consumption and their effects on ECG and hemodynamic parameters, 18 healthy volunteers consumed 32 oz. of ED or caffeinated control drink, both containing 320 mg of caffeine. The time-matched, baseline-adjusted changes in QTc interval and BP were compared at 0, 1, 2, 4, 6, and 24 hours after drink consumption. There was a significantly greater increase in QTc interval from baseline in the ED group than the
caffeine arm at 2 hours (p=0.02), as well as an increase in SBP at 6 hours post-drink (p=0.01) 
(Fletcher et al., 2017).

Another randomized, double-blind, placebo-controlled, crossover study investigated the 
effects of drinking multiple EDs daily for 7 days on blood pressure and ECG parameters. 
Participants were instructed to drink 1 bottle of 5-Hour Energy® (200 mg/2 oz.) twice daily for 
7 days or placebo, followed by a 7-day washout period, and then crossover to the opposite study 
drink. The SBP after a single energy shot was significantly higher at 3- and 5-hours post 
consumption (placebo 119±9 mmHg vs. ED 125±10 mmHg at 3 hours [p=0.05], 118±10 mmHg 
vs. 124±9 mmHg at 5 hours [p=0.038]). There were no significant differences between SBP or 
DBP after 7 days of daily ED consumption (Shah, S. A., Dargush et al., 2016).

In a randomized, double-masked, placebo-controlled crossover study, 34 healthy 
participants each consumed 32 oz. of two types of EDs and placebo on 3 study days with a-6-day 
washout period in between each treatment. Both EDs were commercially available products. The 
maximum change from baseline in QTcB interval for drink A was +17.9±9 (P=0.04) and 
+19.6±15.8 for drink B (P<0.01). The maximum change from baseline in peripheral SBP was 
15.9±5 for drink A (P<0.001) and 14.4±4.8 mmHg for drink B (P<0.001). Significant increases 
in peripheral DBP and central SBP, and central DBP were also noted (Shah, S. A. et al., 2019).

Another biomarker for cardiovascular health that was studied was endothelial function 
through endothelium-dependent flow mediated dilation (FMD), a non-invasive method to 
evaluate early changes in vascular function in systemic arteries. Endothelial dysfunction, 
particularly leading to a reduction in nitric oxide, is a strong predictor of future cardiovascular 
events. Endothelium-derived nitric oxide functions as antiatherogenic molecules that enhances 
vasodilation, reduces platelet aggregation, prevents smooth muscle proliferation, and inhibits 
leucocyte adhesion (Yuyun, Ng, & Ng, 2018). In one study that investigated the acute effects of 
ED consumption on arterial endothelial flow-mediated dilation, eleven healthy volunteers 
underwent baseline testing of endothelial function through endothelium-dependent FMD with
high-resolution ultrasound, drank one 24-oz. ED, and remeasured FMD. The results show a significantly attenuated peak FMD response after ED consumption, which may be associated with an acute significant impairment in endothelial function (Higgins, John P. et al., 2017).

**Current Epidemiology of Diabetes, Hypertension, and Obesity**

Diabetes mellitus (DM) and hypertension (HTN) were both leading causes of deaths in 2015 in the US at rank 7 and 13, respectively (National Center for Health Statistics, 2017). Both diseases are significant risk factors for cardiovascular disease, stroke, and kidney failure. According to the Centers for Disease Control and Prevention (CDC), about 1 in 3 American adults have HTN and only about 54% of those have controlled BP. Complications arising from uncontrolled HTN include stroke, myocardial infarction, cardiomyopathy, and eclampsia in pregnant women. Approximately 1 in 9 American adults are diagnosed with DM, and the incidence has tripled in the last 20 years as more Americans age and become overweight or obese. Microvascular and macrovascular complications from DM include risk of peripheral neuropathy, nephropathy, stroke, myocardial infarction, infections, and limb amputations.

In addition to high caffeine content, ED also has high amount of sugars, ranging from 25-50 grams per drink (National Center for Complementary and Integrative Health, (NCCIH), 2017). Each 8-oz. serving of Monster® and Red Bull® contains approximately 27 g of sugar (US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory, 2017a) (US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory, 2017b). With container sizes ranging from 8- to 24-oz, EDs can significantly contribute to daily sugar intake for the chronic consumer. Consuming 1-2 servings of sugar-sweetened beverages, including EDs, have been found to significantly increase the risk of developing type 2 DM by 26% (risk ratio [RR] 1.26, CI 1.12-1.41) and metabolic syndrome by 20% (RR 1.2 [1.02-1.42]) (Malik et al., 2010).

In addition to public health concerns regarding chronic diseases, such as hypertension and diabetes, obesity continues to steadily increase in the US. It is estimated that 17.2% of US
children and adolescents and 20.7% of US adults were obese in 2014 (National Center for Health Statistics, 2017). The age-adjusted percentage of US adults with grade 3 obesity (Body Mass Index [BMI] > 40) has more than doubled from 2.9% to 7.6% in the last 20 years. This is a growing concern as obesity is a significant risk factor for cardiovascular diseases, diabetes, and cancer. Literature reviewing the impact of sugar-sweetened beverages show that one daily serving is associated with increased BMI and weight gain in children and adults. (Malik, Pan, Willett, & Hu, 2013) Furthermore, teens who reported using EDs at least once within the last week had significantly higher BMI when compared to non-ED users (21.99 kg/m² ± 0.23 vs. 21.11 kg/m² ± 0.02, p=0.004) (Williams, Housman, Odum, & Rivera, 2017). These adolescents were also more likely to consume other high-sugar beverages, compared to teens who reported no past 7-day use of ED.

**Objective and Purpose**

The purpose of this study is to investigate the cardiovascular and metabolic effects of chronic consumption of ED in a healthy population, including BP, ECG, fasting blood glucose (FBG), fasting lipid panel (FLP), weight, BMI, and body fat composition. The primary objective is to compare the systolic BP before and after 4-weeks of daily consumption of EDs. Secondary objectives are to compare the ECG, FBG, FLP, weight, BMI, body fat composition parameters, and serum creatinine before and after 4-weeks of daily consumption of EDs.

**Hypothesis**

The hypothesis is that chronic ED consumption leads to elevated BP. Additionally, chronic ED consumption may also lead to increases in QTc interval, FBG, FLP, weight, BMI, and body fat. These are biomarkers that may imply that daily ED consumption may increase the risk of hypertension, arrhythmias, diabetes, as well as weight gain/obesity.
Chapter 3: Materials and Methods

Study Oversight

**IRB approval.** This study involved human subjects, and thus a research application and proposal to determine eligibility of the research was submitted to the University of the Pacific (UOP) Institutional Review Board (IRB).

**Informed consent.** Participants provided informed consent using the form approved by the IRB. This form included information regarding the purpose of the study, how the research would be conducted, eligibilities to participate in the study, procedures to be carried out by the investigator and the participant, expected duration of the individual’s participation, any foreseeable risks of the study, information regarding compensation for participation, information regarding voluntary withdrawal from the study, confidentiality statement, and contact information of the primary study investigator. Prior to study enrollment, study investigators clarified any concerns and questions from the participant. Once the participant understood the expectations and risks associated with the study, he/she signed the informed consent form and was given a completed copy.

**Risk management.** Participants were observed for any adverse events during the study and followed throughout the 4-week study period. Safeguards were implemented to minimize risk of adverse events. In the event of minor adverse events, study investigators assisted participants to determine if further medical care was needed and provided instructions and/or referrals to appropriate medical facility, if necessary. In the event of serious adverse events, participants were instructed to contact emergency services immediately for medical care.

All participants were provided with the primary investigator’s contact information to contact during normal business hours to discuss any adverse events they may be experiencing while offsite. Withdrawal of participants from the study occurred if the participants experienced a serious adverse event that required evaluation by medical professionals who recommended
study withdrawal. Any serious adverse events that occurred during the study were reported to the University of the Pacific IRB in a timely manner.

**Study Population**

**Recruitment.** For participant recruitment, flyers and emails were distributed within the UOP community. Locations include UOP campuses, San Joaquin Delta College, and local businesses. Emails were also sent to the UOP Pharmacy and Health Sciences students, staff and faculty.

**Inclusion/exclusion criteria and screening.** After study participants were consented, eligibility for study participation was determined during the screening visit. Healthy volunteers with no medical conditions between the age of 18 and 40 years old were enrolled. Participants were excluded if they had any risk factors for cardiovascular disease, such as known history of cardiac arrhythmias, prolonged baseline corrected QT (QTc) interval (greater than 440 ms for males or 460 ms for females), family history for premature sudden cardiac death before age of 60 years, cardiomyopathy, and atherosclerosis. Other exclusion criteria include caffeine-naïve consumers (defined as < 2 cups of coffee [or equivalent caffeine intake] per week), chronic high-caffeine consumers (>7 cans of EDs [or equivalent caffeine intake] per week), history of substance abuse, renal or hepatic dysfunction, concurrent use of drugs or over-the-counter products that may interact with study drinks, baseline blood pressure (BP) greater than 130/80 mmHg, baseline fasting blood glucose (BG) greater than 126 mg/dL, pregnancy, or lactation. Participants were also excluded for any refusal to sign informed consent form or unwillingness to follow study protocol and if they had any procedures that may interfere with the continuous ECG monitoring, such as magnetic resonance imaging and neuromuscular stimulators.

Other baseline information collected during the screening process include age, height, weight, sex, ethnicity, typical consumption of caffeinated drinks, average daily amount of sleep, and average weekly amount of physical activity. Baseline measurements of electrocardiogram
ECG), BP, and fasting BG were obtained to rule out participants that may meet exclusion criteria. Pregnancy tests were also administered for all female participants who are capable of being pregnant.

Once the participant was deemed to have met all inclusion and exclusion criteria, the participant was enrolled, and study protocol was initiated.

**Study Design and Interventions**

This study was a unblinded, non-randomized, proof-of-concept, prospective study to evaluate the effects of chronic consumption of energy drinks in a healthy population. Each participant consumed two 16 oz. cans of a commercially available ED daily in two divided doses for 28 days. Each 16-oz. can of ED contained 320 mg of caffeine, 54 g of sugar, 210 calories, 3.4 mg of riboflavin, 40 mg of niacin, 4 mg of vitamin B6, 12 mcg of vitamin B12, 2000 mg of taurine, 400 mg of panax ginseng, and 2500 mg of “energy blend” (L-carnitine, glucose caffeine, guarana, inositol, glucuronolactone, and maltodextrin). Study products were purchased from standard vendors and dispensed untampered.

Investigators met with participants on days 0, 7, 14, 21, and 28 of the study. At each visit, participants were given instructions to drink 2 cans of energy drinks daily in two divided doses. Participants were required to fill out a standardized log of consumption, which included date and time of consumption, as well an estimate of additional caffeine intake. Participants were cautioned of the FDA recommended caffeine limit of 400 mg/day and provided a reference sheet with estimated caffeine content in common foods and drinks. The following measurements were taken for each participant over the 28 days: BP, ECG, FBG, FLP, weight, BMI, body fat composition, and serum creatinine. Participants were expected to meet with the investigator and/or study personnel once every week for 4 weeks for measurements, as well as picking up a week supply of ED.

On days 0 and 28 the following measurements were taken at baseline: BP, ECG, FBG, FLP, weight, body fat composition, and serum creatinine. On days 0, 7, 14, 21, and 28, an
additional BP and ECG were taken 1 hour after consuming 1 can of ED (after the baseline readings). On day 14, the following additional measurements were taken: FBG, weight, BMI, and body fat composition. Each appointment for measurements ranged from 1.5 – 2 hours per session. All measurements were recorded in the participant data collection form. Participants were also asked to note any adverse effects, as well as activity and stress levels, throughout the study.

**Study Measurements**

**Electrocardiography.** A standard 12-lead ECG machine (Philips PageWriter Trim III, Philips Medical Systems, Andover, MA) was used to obtain QT interval, PR interval, and QRS duration. QT interval obtained was further corrected for heart rate extremes to QTc with Bazett’s and Fridericia’s equations. Calibration of the ECG machine was performed and used the standard setting of 1-milliVoltage/centimeter with a paper speed of 25 millimeter/second.

**Blood pressure and heart rate.** Peripheral and central systolic and diastolic BP, as well as heart rate, were measured using a standard blood pressure brachial cuff monitor with noninvasive pulse wave analysis (SphygmoCor XCEL® PWA System, AtCor Medical Pty Ltd, West Ryde, Australia). Participants were instructed to rest 10 minutes prior to measurements. Participants were instructed to be seated upright with feet flat on the floor and arm flexed at heart level. All BP and heart rate measurements were taken twice (two minutes apart) and averages will be calculated for analysis.

**Weight and body composition.** Height and baseline fasting weight were obtained at each visit and used to calculate participant’s BMI. Weight, BMI and body composition, including body fat percentage, fat mass, muscle mass, and bone mass, was measured with the MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita®, Arlington Heights, IL) at each visit.

**Fasting blood glucose, fasting lipid panel, and serum creatinine.** FBG was measured using a standard glucometer (Precision Xtra®, Abbott Diabetes Care Inc., Alameda,
CA). FLP and serum creatinine was measured using a point-of-care tool (CardioChek® Plus Analyzer, PTS Diagnostics, Indianapolis, IN), which requires a fingerstick blood sample.

**Adverse events.** Participants were observed and interviewed for any signs and symptoms of adverse events related to cardiovascular, gastrointestinal, and central nervous systems that may be related to the study product. Anticipated cardiovascular adverse effects included tachycardia, elevated blood pressure, flushing, and palpitations. Gastrointestinal adverse effects included nausea, vomiting, diarrhea, upset stomach, and loss of appetite. Central nervous system adverse events included agitation, hallucination, headache, insomnia, irritability, restlessness, dizziness, and confusion.

**Data Analysis**

**Study endpoints.** Given the possibility of high drop-out rates, data analysis was conducted with the intention-to-treat approach, using the last observation carried forward methodology. The primary endpoint of the study to assess the maximum change in peripheral systolic BP (pSBP), as compared to baseline pSBP, during the 28-day of ED consumption. Secondary endpoints include maximum changes between peripheral diastolic BP (pDBP), central SBP (cSBP), central DBP (cDBP), HR, Augmentation Index (normalized at heart rate of 75 [Aix@75]), QTc interval, fasting blood glucose (BG), fasting lipid panel (which includes total cholesterol [TC], high density lipoprotein [HDL], low density lipoprotein [LDL], triglycerides [TG]), BMI, body fat analysis, and serum creatinine (SCr) during the study period. Any adverse events were recorded.

**Power calculation.** To detect a significant difference in peripheral SBP of 4 mmHg (assuming a standard deviation of 4 mmHg, alpha value of 0.05, power of 80%), ten participants would be needed to participate in the study.

**Statistical analysis.** Baseline characteristics and endpoints were reported using descriptive statistics: frequencies and percentages for discrete variables and means and standard deviations for continuous variables. Wilcoxon signed-rank test was used to compare
and detect statistical difference between endpoints for baseline vs. maximum post-dose BP, maximum post-dose QTc, BG, FLP, weight, BMI, body fat, and serum creatinine values. Data collection and analysis were performed with Microsoft Excel for descriptive statistics (Version 16.10, Microsoft, Redmond, WA) and SPSS for all other statistics (Version 26, IBM Corporation, Armonk, New York).
Chapter 4: Results

Study Population

Sixteen participants were initially screened for eligibility to participate in the study. One participant was excluded due to history of substance use, and one participant was excluded due to high chronic caffeine consumption (>2,240 mg of caffeine/week). A total of 14 participants were enrolled between February 2019 and June 2019. A total of 12 participants completed the study (Figure 1). One participant dropped out of the study due to adverse effects, and one participant dropped out of the study due to undisclosed personal reasons.

Baseline characteristics (Table 1) showed a majority of the participants were male (86%). The population was demographically diverse, with 43% Asian, 29% Hispanic, 21% Caucasian, and 7% African-American. The median reported hours of sleep per day was 7 hours (range 5-11) and median reported physically active days during the week was 4.5 days (range 2-7). The median estimated caffeine intake during the week was 425 mg (range 87-1120). Majority of the participants do not consume EDs (64.3%). Among the ED consumers, about 40% report drinking 1-2 cans of EDs during the week, 20% drinking 3-4 cans of EDs, and another 40% drinking ≥ 5 cans of EDs. Majority of the participants had normal BMI (57%), with 29% classified as overweight and 14% classified as obese.
Figure 1: Participants who were enrolled and included in data analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Participants (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yr</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>21 (19 – 39)</td>
</tr>
<tr>
<td><strong>Sex – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (14%)</td>
</tr>
<tr>
<td><strong>Race or ethnicity – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>African-American</td>
<td>1 (7%)</td>
</tr>
<tr>
<td><strong>Hours of sleep – hr</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>7 (5 – 11)</td>
</tr>
<tr>
<td><strong>Active days during week – days</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.5 (2 – 7)</td>
</tr>
<tr>
<td><strong>Estimated caffeine intake per week – mg</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>425 (87 – 1120)</td>
</tr>
<tr>
<td><strong>Number of ED consumed per week – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (64.3%)</td>
</tr>
<tr>
<td>1-2</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>3-4</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>≥5</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td><strong>Baseline BMI classification</strong></td>
<td></td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Overweight (25.0-29.9)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Obese (≥30.0)</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>
Cardiovascular Endpoints

**SphygmoCor PWA endpoints.** Table 2 summarizes the mean baseline and mean maximum measurements in the SphygmoCor PWA endpoints. Maximum measurements in pSBP, pDBP, cSBP, cDBP, HR, and Aix@75 were found to be statistically significantly higher than baseline measurements (all P<0.05). The average maximum change from baseline to maximum pSBP, pDBP, cSBP, and cDBP was 9±7 mmHg, 5±4 mmHg, 7±6 mmHg, 5±4 mmHg, respectively. Figure 2 summarizes the mean BPs, HR, and Aix@75 on days 0, 7, 14, 21, and 28.

Due to two participant drop-outs, a per protocol analysis was conducted. Similarly, there was statistically significant difference between baseline and maximum measurements in pSBP, pDBP, cSBP, cDBP, HR, and Aix@75 (all P<0.05) (Table 3).

For pSBP, a statistically significant difference was noted between baseline and days 21 and 28 with an average increase of 5±7 mmHg on Day 21 and 6±7 mmHg on Day 28 (P=0.017 and P=0.022, respectively). There were no statistically significant differences between baseline and subsequent days in pDBP, cSBP, and cDBP. It is notable that HR was significantly increased compared to baseline on days 14, 21, and 28 with an average increase of 6±6 bpm, 6±8 bpm, and 5±7 bpm (P=0.009, P=0.01, P=0.026, respectively). During the study period, one participant had peripheral BP >140/80 mmHg while three participants had BP > 130/80 mmHg. No significant differences were detected between baseline and subsequent days for Aix@75.
Table 2: Intention-to-treat maximum change in SphygmoCor PWA endpoints (N=14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean baseline (±SD)</th>
<th>Mean max (±SD)</th>
<th>Maximum change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral SBP (mmHg)</td>
<td>119 (±5)</td>
<td>129 (±7)</td>
<td>9 (±7)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Peripheral DBP (mmHg)</td>
<td>75 (±5)</td>
<td>79 (±5)</td>
<td>5 (±4)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>107 (±4)</td>
<td>114 (±6)</td>
<td>7 (±6)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Central DBP (mmHg)</td>
<td>76 (±5)</td>
<td>81 (±4)</td>
<td>5 (±4)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64 (±8)</td>
<td>74 (±9)</td>
<td>11 (±6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Aix@75</td>
<td>7 (±10)</td>
<td>14 (±14)</td>
<td>8 (±8)</td>
<td>0.024*</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: SBP = systolic blood pressure, Aix@75 (Augmentation Index corrected at heart rate of 75 bpm)

Table 3: Per-protocol maximum change in SphygmoCor PWA endpoints (N=12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean baseline (±SD)</th>
<th>Mean max (±SD)</th>
<th>Maximum change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral SBP (mmHg)</td>
<td>120 (±5)</td>
<td>129 (±7)</td>
<td>9 (±7)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Peripheral DBP (mmHg)</td>
<td>75 (±5)</td>
<td>79 (±5)</td>
<td>5 (±4)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>107 (±4)</td>
<td>114 (±6)</td>
<td>7 (±6)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Central DBP (mmHg)</td>
<td>76 (±5)</td>
<td>81 (±5)</td>
<td>5 (±4)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64 (±9)</td>
<td>73 (±10)</td>
<td>9 (±5)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Aix@75</td>
<td>6 (±10)</td>
<td>16 (±13)</td>
<td>10 (±5)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: SBP = systolic blood pressure, Aix@75 (Augmentation Index corrected at heart rate of 75 bpm)
Figure 2: Mean SphygmoCor® endpoints by study day. (a) Mean peripheral systolic blood pressure (pSBP) (b) Mean peripheral diastolic blood pressure (pDBP) (c) Mean central systolic blood pressure (cSBP) (d) Mean central diastolic blood pressure (cDBP) (e) Mean heart rate by day. (f) Mean Augmentation Index corrected at heart rate of 75 bpm (Aix@75)
**Electrocardiogram endpoints.** Figure 3 presents the mean electrocardiogram endpoints on days 0, 7, 14, 21, and 28. Table 4 summarizes the mean baseline and maximum measurements in QTcB interval, QTcF interval, RR interval, PR interval, and QRS duration. Maximum measurements for QTcB and QTcF intervals were found to be statistically higher than baseline (both $P=0.001$). The average maximum change from baseline in QTcB interval was $19\pm13$ ms, which is similar to an average maximum change of $15\pm10$ ms in QTcF interval. Both QTcB and QTcF intervals on days 7, 14, 21, and 28 were all found to be significantly higher than baseline (all $P<0.05$) (Table 5).

During the study period, one female had a prolonged QTcB interval of 468 ms on day 14, with an increase of 34 ms from baseline. Two males had a prolonged QTcB interval of 441 and 447 ms on day 21, with an increase of 8 and 15 ms from baseline, respectively. Four participants had clinically significant increases in QTcB interval $>30$ ms from baseline during the study period. No participants had QTc interval increases $>50$ ms from baseline during the study.

While there were no statistically significant maximum changes in RR, PR, and QRSd in the intention-to-treat analysis, mean max of RR interval was found to be significantly higher than baseline ($P=0.015$) (Table 6).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean baseline (±SD)</th>
<th>Mean max (±SD)</th>
<th>Maximum change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcB (ms)</td>
<td>413 (±19)</td>
<td>433 (±13)</td>
<td>19 (±13)</td>
<td>0.001*</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>413 (±20)</td>
<td>427 (±16)</td>
<td>15 (±10)</td>
<td>0.001*</td>
</tr>
<tr>
<td>RR (ms)</td>
<td>978 (±102)</td>
<td>1026 (±145)</td>
<td>47 (±120)</td>
<td>0.158</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>150 (±20)</td>
<td>151 (±20)</td>
<td>1 (±5)</td>
<td>0.753</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>97 (±8)</td>
<td>99 (±8)</td>
<td>2 (±4)</td>
<td>0.152</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: QTcB = corrected QT interval using Bazett’s equation, QTcF = corrected QT interval using Fridericia’s equation
Table 5: Mean QTc intervals during study period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (±SD)</th>
<th>Difference from baseline (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcB (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (baseline)</td>
<td>413 (±19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>425 (±12)</td>
<td>11 (±15)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Day 14</td>
<td>425 (±16)</td>
<td>12 (±16)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Day 21</td>
<td>427 (±15)</td>
<td>13 (±9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Day 28</td>
<td>424 (±14)</td>
<td>10 (±13)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Max</td>
<td>433 (±13)</td>
<td>19 (±13)</td>
<td>0.001*</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 (baseline)</td>
<td>413 (±21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>421 (±14)</td>
<td>9 (±13)</td>
<td>0.046*</td>
</tr>
<tr>
<td>Day 14</td>
<td>419 (±16)</td>
<td>6 (±10)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Day 21</td>
<td>423 (±19)</td>
<td>10 (±8)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Day 28</td>
<td>421 (±14)</td>
<td>9 (±11)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Max</td>
<td>427 (±16)</td>
<td>15 (±10)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: QTcB = corrected QT interval using Bazett’s equation, QTcF = corrected QT interval using Fridericia’s equation

Table 6: Per-protocol maximum change in electrocardiogram endpoints (N = 12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean baseline (±SD)</th>
<th>Mean max (±SD)</th>
<th>Maximum change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcB (ms)</td>
<td>414 (±18)</td>
<td>432 (±14)</td>
<td>17 (±12)</td>
<td>0.003*</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>413 (±20)</td>
<td>427 (±17)</td>
<td>15 (±7)</td>
<td>0.002*</td>
</tr>
<tr>
<td>RR (ms)</td>
<td>968 (±106)</td>
<td>1049 (±142)</td>
<td>82 (±120)</td>
<td>0.015*</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>147 (±20)</td>
<td>147 (±20)</td>
<td>1 (±5)</td>
<td>0.844</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>95 (±4)</td>
<td>97 (±4)</td>
<td>1 (±4)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: QTcB = corrected QT interval using Bazett’s equation, QTcF = corrected QT interval using Fridericia’s equation
Figure 3: Mean electrocardiogram endpoints by day. (a) Mean corrected QT interval using Bazett’s equation (QTcB) (b) Mean corrected QT interval using Fridericia’s equation (QTcF) (c) RR interval (d) PR interval (e) QRS duration (QRSd)
**Metabolic Endpoints**

Table 7 summarizes the maximum change in fasting blood glucose and body composition analysis. There was a statistically significant increase in maximum FBG from baseline with an average increase 4±9 mg/dL (P=0.048). The mean FBG on day 0 was 92±8 mg/dL, 93±8 mg/dL on day 14, and 94±9 mg/dL on day 28. No participants had FBG > 126 mg/dL during the study period. No detectable statistically significant differences were found between the various body composition analysis endpoints, including weight, BMI, percentage of body fat, fat mass, muscle mass, bone mass, and visceral fat rating.

About 64% of participants had higher weight at Day 28 than baseline. Similarly, 64% of participants had an increase in their BMI at Day 28, compared to their baseline BMI. About 70% of participants had an increase in their maximum percentage of body fat during the study period, with 57% had an increase in their maximum fat mass from baseline. About 64% of participants had an increase in muscle mass during the study period and 57% had an increase in bone mass during the study period.

Due to machine error, several fasting lipid panels had missing measurements for various parameters. This occurred in 3 participants. There were no statistically significant difference between baseline and day 28 serum creatinine and fasting lipid panel parameters, including total cholesterol, high-density lipoproteins, low-density lipoproteins, and triglycerides (Table 8). About 64% of participants had an increase in total cholesterol, and about 67% of participants had an increase in triglycerides at day 28. One participant had noted total cholesterol > 200 mg/dL during the study period.
Table 7: Intention-to-treat† maximum change in blood glucose and body composition analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean baseline (±SD)</th>
<th>Mean max (±SD)</th>
<th>Maximum change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL)</td>
<td>92 (±8)</td>
<td>97 (±8)</td>
<td>4 (±9)</td>
<td>0.048*</td>
</tr>
<tr>
<td>Weight (lbs.)</td>
<td>169.5 (±35.7)</td>
<td>170.3 (±36.7)</td>
<td>0.8 (±2.4)</td>
<td>0.221</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (±5)</td>
<td>24 (±5)</td>
<td>0 (±0)</td>
<td>0.131</td>
</tr>
<tr>
<td>Percentage of body fat (%)</td>
<td>19.9 (±9.6)</td>
<td>20.6 (±9.4)</td>
<td>0.7 (±1.5)</td>
<td>0.157</td>
</tr>
<tr>
<td>Fat mass (lbs.)</td>
<td>35.5 (±23)</td>
<td>36.1 (±23)</td>
<td>0.6 (±1.5)</td>
<td>0.107</td>
</tr>
<tr>
<td>Muscle mass (lbs.)</td>
<td>127.1 (±21.2)</td>
<td>128.3 (±21.1)</td>
<td>1.2 (±2.4)</td>
<td>0.109</td>
</tr>
<tr>
<td>Bone mass (lbs.)</td>
<td>6.7 (±1.1)</td>
<td>6.8 (±1.1)</td>
<td>0.1 (±0.2)</td>
<td>0.088</td>
</tr>
<tr>
<td>Visceral fat rating</td>
<td>4 (±4)</td>
<td>4 (±4)</td>
<td>0 (±0.6)</td>
<td>1</td>
</tr>
</tbody>
</table>

*p-value < 0.05; Abbreviations: FBG = fasting blood glucose, BMI = body mass index
†N = 14

Table 8: Per-protocol† comparison of baseline vs. day 28 of FLP and serum creatinine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (±SD)</th>
<th>Day 28 (±SD)</th>
<th>Mean change (±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>157 (±36)</td>
<td>152 (±36)</td>
<td>-5 (±30)</td>
<td>0.505</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>48 (±11)</td>
<td>48 (±10)</td>
<td>0 (±6)</td>
<td>1</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>97 (±34)</td>
<td>89 (±36)</td>
<td>-8 (±32)</td>
<td>0.635</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>115 (±38)</td>
<td>125 (±72)</td>
<td>10 (±66)</td>
<td>0.678</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.34 (±0.32)</td>
<td>1.55 (±0.34)</td>
<td>0.22 (±0.42)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

Abbreviations: HDL = high-density lipoproteins, LDL = low-density lipoproteins, TG = triglycerides
†N = 12
Adverse Effects

Table 9 summarizes the various adverse effects reported by participants during the study. No participants reported any serious adverse effects that required medical attention. All participants reported at least one side effect that was related to the central nervous system (CNS), with the most common CNS effects being jitteriness (78.6%) and feeling energized/alert (78.6%), followed by fatigue (57.1%) and energy crash (50%). Most energy crashes were noted to be post-drink and/or in the late afternoons. Three participants reported acute paresthesia shortly after finishing the ED, often described as a tingling sensation in the hands or throughout the body. Three participants reported developing a craving for EDs, with one participant describing the craving as “feeling addicted.”

The most common gastrointestinal effect reported was an upset stomach and reduced or loss of appetite (Table 9). Upset stomach was most commonly associated with drinking the ED on an empty stomach. Five participants reported a change in urine color post-drink, described as a bright, green color. The green urine was not persistent through the day, but most associated within a few hours after drinking the ED. The most common cardiovascular adverse effect was a fast heart rate. Two participants reported post-drink tachypnea or dyspnea at rest or during active exercise.
Table 9: Reported adverse effects during study period

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Number of participants (N=14) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Jitteriness</td>
<td>11 (78.6%)</td>
</tr>
<tr>
<td>Energized/alert</td>
<td>11 (78.6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (57.1%)</td>
</tr>
<tr>
<td>Energy crash</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Agitation/restlessness</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Cravings</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Light-headedness/dizziness</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal System</strong></td>
<td></td>
</tr>
<tr>
<td>Upset stomach</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Reduced/loss of appetite</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>Bloating</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Thirst</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td><strong>Genitourinary System</strong></td>
<td></td>
</tr>
<tr>
<td>Green urine</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
</tr>
<tr>
<td>Fast heart rate</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea/tachyplea</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 (7.1%)</td>
</tr>
</tbody>
</table>
Chapter 5: Discussion

To our knowledge, this is the longest study investigating the cardiometabolic effects of chronic ED consumption. The results show that daily consumption of 2 cans of ED/day for 28 days significantly increases blood pressure and heart rate, as well as QTc interval and fasting blood glucose. Previous studies have demonstrated significant elevations in blood pressure and QTc interval with acute ED consumption. However, this study supports the hypothesis that chronic ED consumption may have long-term impact on blood pressure elevations and QTc prolongation.

Hypertension continues to be a major public health concern in the United States, as the prevalence was found to significantly increase with age from 2014-2015 and 2015-2016 (Fryar, Ostchega, Hales, Zhang, & Kruszon-Moran, 2017; Murphy, Xu, Kochanek, Curtin, & Arias, 2017). Studies have demonstrated that beginning at BP 115/75 mmHg, cardiovascular disease risk, as well as mortality from both ischemic heart disease and stroke, double for each incremental increase of 20/10 mmHg (Chobanian et al., 2003). Small incremental changes as minimal as 1 mmHg increase in untreated SBP has been correlated with 1% increase risk of stroke death (Palmer et al., 1992). Most recently, the 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults has redefined blood pressure categories to normal BP as <120/<80 mmHg and elevated BP as 120-129/<80 mmHg. Hypertension was also redefined with Stage 1 HTN as having a SBP of 130-139 or DBP of 80-89 mmHg and Stage 2 HTN as having a SBP ≥140 or DBP ≥90 mmHg (Whelton et al., 2018). Given our study results showing significantly higher pSBP on days 21 and 28 than baseline (mean pSBP at 125±9 mmHg and 125±8 mmHg, respectively), it suggests that chronic ED consumption may lead to sustained elevated BP.

The average increase in peripheral SBP from baseline ranged from 4 to 6 mmHg during the study. Previous studies on the effects of chronic coffee consumption have demonstrated
smaller BP elevations (about +2/1 mmHg) and concluded this BP elevation caused by chronic coffee consumption is not associated with developing HTN (Geleijnse, 2008; Klag et al., 2002). The John Hopkins Precursors Study assessed coffee intake in over 1,000 former students over a median of 33 years follow-up time and found that coffee-drinking is associated with only small increases in BP (+0.19 mmHg/0.27 mmHg for 1 cup of coffee/day), but not associated with the development of HTN (Klag et al., 2002). However, given the evidence from Fletcher et al. (2017) showing that the degree of BP elevation differs between ED and caffeine, the differences in ingredients of EDs compared to coffee and caffeine may impact the risk of developing long-term consequences from chronic use, including HTN.

QTc prolongation is a known risk factor for potentially fatal arrhythmias, including torsades de pointes. While prolonged QTc is defined as > 450 ms for males and > 470 ms for females, a QTc interval > 500 ms or an increase in QTc > 30 ms requires careful monitoring and is most likely proarrhythmic (Li & Ramos, 2017; Shah, R. R., 2002). Each 10-ms increase in QTc interval is also associated with 6% increased risk of torsades (Zareba et al., 1998). Risk factors for torsades de pointes include age > 65 years old, bradycardia, electrolyte abnormalities (i.e. hypokalemia, hypomagnesemia, hypocalcemia), genetic predisposition, congenital long QT syndrome or genetic polymorphisms, heart disease, and concomitant use of more than one known QT-prolonging agents (Li & Ramos, 2017). This is potentially life-threatening for already at-risk ED consumers, as the use of another QT-prolonging substance may compound and increase their QTc interval into a torsadogenic range. Several studies have demonstrated the significant acute effects of QTc prolongation following ED consumption (Basrai et al., 2019; Fletcher et al., 2017; Shah, S. A., Occiano et al., 2016; Shah et al., 2019). In this study, there were significant sustained increases in QTc intervals from baseline throughout the study, from days 7 to 28. On average the increase in QTcB from baseline ranged from 10 to 13 ms. This study adds to the current evidence that suggest EDs can prolong QTc and increase the risk of life-threatening arrhythmias.
While our study did not show any significant findings in fasting lipid panel and body composition changes, there was a significant difference between maximum change in fasting blood glucose, compared to baseline. The American Diabetes Association defines the diagnostic criteria for diabetes as having a FBG ≥ 126 mg/dL, a 2-hour BG ≥ 200 mg/dL during an oral glucose tolerance test, A1c ≥ 6.5%, or a random BG ≥ 200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis (American Diabetes Association, 2019). Given that most EDs contain about 25-50 g of sugar, having participants drink 2 cans of ED per day greatly increased their daily consumption of sugars. While our study was unable to detect clinically relevant increases in FBG, there is evidence that acute ED consumption may decrease insulin sensitivity. In one study, ED induced a significantly low reduction of glucose concentration (P<0.05) and a marked increase in serum insulin (P<0.001) and HOMA-IR, a calculated index for insulin resistance (P<0.001), at 1 hour post-consumption of 1000 mL (33 oz) of ED (Basrai et al., 2019).

**Study Limitations**

There were several limitations to this study. First, this study only studied 2 cans of EDs twice daily, which may not be representative of the general population’s real-world ED consumption pattern. There are various volume sizes available, ranging from 12 to 24 oz. cans, as well as differences in various caffeine, sugar, and other supplement content. Also, generalizability is limited due to the small sample size made up of mostly healthy young adult male students. Lifestyle differences, including exercise habits, diets, and stress levels, may affect individual response to EDs.

Furthermore, any deviation to study protocol was difficult to identify and control. In an effort to verify adherence, participants were instructed to complete a log of their ED consumption time, adverse effects, estimated additional daily caffeine intake, and any active or strenuous exercise. However, despite reminders and repetitions of instructions, several participants disclosed instances of nonadherence. One participant had reported that due to a
misunderstanding, he had fasted and refrained from caffeine 24 hours prior to his day 7 study appointment, thus missing one dose of ED. Another participant had reported that she had replaced one of her doses with a different brand of ED due to forgetting her provided supply at home.

Another limitation of the study includes the variations of additional caffeine intake among participants. While study investigators discouraged any caffeine intake greater than the FDA recommendation of 400 mg/day, at least two participants reported additional caffeine intake from various sources, including caffeinated sodas and other brands of ED. No adverse effects were noted for these participants. Participants may also be unaware of caffeine content in other foods and supplements. Popular products, such as pre-workout supplements, may range from 90 to over 300 mg of caffeine per serving (Desbrow et al., 2019).

Another problematic issue that was encountered were errors in measurements due to limitations in laboratory equipment. The range of measurement for total cholesterol on the point-of-care instrument was 100-140 mg/dL. In several cases, the total cholesterol resulted as <100 mg/dL, which lead to discrepancies in measuring triglycerides and calculated LDL parameters. Sampling larger volume of whole blood samples in traditional laboratory testing may bypass this issue.

In addition, this proof-of-concept study did not include a placebo arm, which would be prudent to compare and ensure that the changes in different parameters were indeed the result from consuming EDs.

**Future Direction**

Further studies should be conducted to include a more diverse population, including females, to ensure inclusion of various genetic polymorphisms that may affect an individual’s response to EDs. Also, continuous ambulatory ECG monitoring would be ideal to capture a longer timeframe and possible dysrhythmias that may occur outside of the study day. It may be possible that certain arrhythmias may be transient and only manifests under certain stressful
conditions, including strenuous exercise. In addition, additional metabolic markers should be included, such as hemoglobin A1c, to capture long-term changes in glycemic control after adding ED consumption to a participant’s diet.

**Conclusion**

This study demonstrates that chronic energy drink consumption can lead to significant sustained elevations in blood pressure and heart rate, in addition to increases in QTc interval and fasting blood glucose. Our results add to the growing evidence that demonstrate the possible dangers of ED consumption, particularly in at-risk populations. As the popularity of EDs continue to increase, further studies should be conducted to bring awareness and education to the public, as well as possible regulatory measures to include product warnings and sales restrictions to minors.
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Appendix A: Informed Consent Document

Informed Consent

Effects of Chronic Energy Drink Consumption on Cardiometabolic Endpoints

My name is May Chen and I am a pharmacy practice faculty at University of the Pacific, Thomas J. Long School of Pharmacy and Health Sciences. Our research group is recruiting subjects for our study titled “Effects of Chronic Energy Drink Consumption on Cardiometabolic Endpoints”.

This consent form contains information about the purpose of this study, what is expected of you, and the risks and benefits of participation. You should read the information below and ask questions about anything you do not understand before deciding whether or not to participate. If you understand the study and wish to participate, you will need to sign this form. You will also be given a signed copy of this consent to keep.

Your participation in this study is entirely voluntary. You may choose to not participate or choose to withdraw at any time for your own reasons without penalty or loss of benefits.

Purpose

The purpose of this study is to learn if drinking energy drinks everyday may affect a person’s health, particularly its possible effects on the heart, blood pressure, blood sugar, and weight.

Many people use energy drinks regularly, but the overall health concerns are still unknown. There are many energy drink products that contain a mixture of caffeine and other energy-boosting ingredients and supplements which can affect parameters related to the heart, blood pressure and blood glucose. Several previous studies have shown that energy drinks affect heart rhythm and blood pressure significantly. As energy drinks are sugar-sweetened beverages, long-term use may also affect the body’s metabolism, including cholesterol, blood sugars, and weight.

This study involves drinking energy drinks every day for 28 days. We will be conducting several tests, including monitoring and measuring your blood pressure, ECG, fasting blood glucose (sugar), fasting lipid (cholesterol) levels, serum creatinine, weight, and body fat composition. An ECG will measure your heart rhythm. A fasting blood glucose measures your blood sugar when you have not eaten overnight. It is often used to help monitor diabetes and glucose intolerance. A fasting lipid panel will measure your cholesterol, including total cholesterol [TC], high density lipoprotein [HDL], low density lipoprotein [LDL], triglycerides [TG] levels. A serum creatinine test will tell us information about how well your kidney functions.

Each session lasts about 1.5-2 hours and will occur every week with at least 7 days apart from each other. You will have about 8 hours of face-to-face time with the study team through the duration of the study.

To be eligible for this study:

- You must be between 18 years – 40 years of age
- You must be willing to drink 2 cans of energy drinks every day for 28 days
- You must be willing to fast for a limited time prior to your session

You are not eligible to participate in this study if:
● You are younger than 18 years of age or older than 40 years of age
● You have presence of any known medical condition, confirmed through participant interview
● Current use of ANY medication taken on a daily basis (except birth control), to include herbal products or supplements (Daily basis is defined as greater than 2 days per week)
● (Females) You are pregnant or breast-feeding, or planning to get pregnant within next 28 days
● You cannot speak or understand the English language
● You refuse to sign the informed consent form

PROCEDURES

If you agree to participate, you will be one of 18 subjects enrolled in this study. You will be in the study for 28 days. If you choose to enroll, this study will require you to consume two 16-oz. energy drinks every day for 28 days in two separate times (once in the early morning and once in the afternoon).

You will be asked to keep track of when you are drinking the drink each day, any additional caffeinated products during the week, the amount of physical activity during the week, and any adverse effects you may be experiencing from the energy drinks. This log will be collected at every weekly clinic visit. At the clinic visit, your heart rhythm, blood pressure, fasting blood sugar (blood glucose), cholesterol, weight, and body fat composition will be measured. You will also be asked to drink one can of energy drink during the visit, after which your heart rhythm and blood pressure will be monitored 1 hour after finishing the drink.

If you volunteer to participate in this study, we would ask you to do the following things:

Screening Visit (1 hour)
During this visit, we will determine your eligibility for the study. You will not be considered eligible for the study until you have signed the consent form.

It will include a brief interview to ensure you are eligible to participate in the study, followed by an electrocardiogram, also called an ECG. This is performed by placing 12 leads (stickers) on your chest, arms and legs which are then attached to wires that connect to a machine that reads your heart rhythm. In addition, your blood pressure will be taken using a non-invasive standard blood pressure machine used in a doctor’s office and your blood glucose will be measured with a small blood sample using a glucose meter.

If you are female and capable of becoming pregnant, a pregnancy test will be done before you start the study. This will be confirmed by a pregnancy test using your urine, similar to an over-the-counter pregnancy test that you may purchase at a drug store.

If you meet all inclusion requirements, you will be enrolled in the study and be scheduled for the first day of the study. The screening day can also be Day 0.

Day 0 (1.5-2 hours)
- You will be asked to not consume caffeine and alcohol, including energy supplements 48 hours prior to your appointment.
- You will be asked to fast overnight before each study appointment. Fasting means no food or drinks other than water.
- A baseline ECG, blood pressure, fasting blood glucose (BG), cholesterol, serum creatinine, weight, and body fat composition will be obtained.
- Blood pressure measurements will measure both central (at the heart) and peripheral (at the arm) blood pressures. Each measurement will capture both systolic (heart contraction) and diastolic
(heart relaxation) blood pressures. Serum creatinine will be measured via blood prick (cholesterol, and fasting blood glucose measurements would be obtained in the same manner). A serum creatinine test will measure the level of creatinine in your blood and provides an estimate of how well your kidneys filter. Healthy kidneys filter creatinine and other waste products from your blood.

- Then you will consume 1 can of 16-oz energy drink within 15 minutes.
- After 60-minutes, you will have a repeat measurement of your ECG and blood pressure.
- At those times, you will be asked to keep any activity to minimal until the last measurements are collected. You will also be asked to describe any side effects you may be experiencing.
- A 7-day supply of energy drink will be given to you with instructions to drink 1 can between 7:00-10:00AM and another can between 1:00PM-4:00PM every day. You will also be provided the logs to complete and return the following week.
- You will be scheduled for a visit in 1 week.

**Day 7 (1.5-2 hours)**

- You will return completed logs of the past week’s energy drink consumption, caffeine product consumption, physical activity, and any adverse effects related to energy drinks use.
- You will be asked to fast as outlined for Day 0, via e-mail or text reminder
- Your blood pressure and ECG will be obtained, and then you will be asked to drink 1 can of energy drink within 15 minutes.
- Your blood pressure and ECG will be measured 1 hour after the energy drink.
- Another 7-day supply of energy drink will be given to you with the same instructions and log.
- You will be scheduled for a visit in 1 week.

**Day 14 (1.5-2 hours)**

- Same treatment/monitoring process as Day 7 will occur.
- You will be asked to fast as outlined for Day 7, via e-mail or text reminder
- Additional tests will be measured including your fasting blood glucose, weight, BMI, and body fat composition.
- Another 7-day supply of energy drink will be given to you with the same instructions and log.

**Day 21 (1.5-2 hours)**

- Same treatment/monitoring process as Day 7 will occur.
- You will be asked to fast as outlined for Days 7 & 14, via e-mail or text reminder
- Another 7-day supply of energy drink will be given to you with the same instructions and log.

**Day 28 (2 hours)**

- Same treatment/monitoring process as Day 7 will occur.
- You will be asked to fast as outlined for Days 7, 14, and 21, via e-mail or text reminder
- Additional tests will be measured, including your fasting blood glucose, fasting cholesterol, weight, BMI, body fat composition, and serum creatinine.
The following chart summarizes the measurements timeline:

<table>
<thead>
<tr>
<th>Day#</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
</table>

*Taken befor and 1 hour after drink 1 can of ED

*BP measurements will include both central and peripheral blood pressure that captures systolic and diastolic blood pressures

**POTENTIAL RISKS AND DISCOMFORTS**

This study may involve risks that are unpredictable. However, if any new risks become known in the future you will be informed of them. Participation in this study may involve some risks or discomforts, which are listed below.

**Risks**

*Physical - Energy drinks are generally well-tolerated, and its adverse effects are generally mild. Common side effects of the study drinks include upset stomach, nausea, vomiting, diarrhea, bloating, dizziness, flushing, headaches and unpleasant taste. You can experience fast heart rate, high blood pressure, agitation, restlessness, inability to sleep or confusion from the caffeine. You may be more sensitive to the effects of caffeine if you do not consume caffeine regularly. Serious but rare side effects from high dose or heavy use of caffeine have included abnormal heart rhythms, seizures, and other heart-related problems including death. As of 2014, there have been over 30 deaths connected to the use of Energy drinks and the FDA is still looking into the cause of these deaths. There may be other rare risks (e.g. blood clots, vaginal bleeding, serious allergic reactions) from some of the other ingredients along with unknown risks, but the chances are extremely rare. It is possible that your risk for any of the side effects or death may be increased due to consuming the energy drinks consistently for 28 days. It may be possible that you feel tolerance or addiction to energy drinks as a result of consuming them daily for a period of time. This may lead to withdrawal symptoms after stopping the energy drinks. This may be due to the various ingredients in the energy drink, such as caffeine, sugars, and other supplements. Common withdrawal symptoms include headache, fatigue, difficulty concentrating, and dysphoric mood. A gradual reduction in energy drinks over time or low doses of caffeine have been shown to suppress these symptoms.

*Psychological - Expected study duration for each patient is 28 days which may lead to frustration due to following a certain regimen of drink consumption. Potential risk may be associated with effects of energy drink, such as anxiety.

*Loss of confidentiality - There is a possibility that the data could be breached.

**Blood Pressure Monitor**

The use of a blood pressure cuff may cause temporary discomfort for the arm, as you will feel increase in pressure as the machine is reading your blood pressure. The discomfort is generally temporary, as it will disappear at the end of the reading.

**Blood Glucose, Cholesterol, and Serum Creatinine Monitor**

Collecting this small blood sample is has a small risk that is considered minimally invasive. The use of these monitors may cause irritation and/or pain for sensitive patients. It involves a simple fingerstick with a needle and taking a small sample of blood (less than 10 drops of blood). However, the discomfort is generally temporary. Wounds caused by finger pricking may lead to infection; however, this normally is prevented with hygienic and sterile procedures, such as the use of gloves, alcohol swabs, hand washing, and sterile equipment.
**ECG or electrocardiogram.**
The use of adhesive electrocardiogram (ECG) electrodes may cause itching and/or redness under the electrodes in subjects with sensitive skin. This normally resolves when the electrodes are taken off. The adhesive of the electrodes may also cause temporary discomfort for unshaven subjects when electrodes are removed. This can be mitigated by minimizing the amount of hair present and by removing electrodes slowly.

**Pregnancy.**
If you are pregnant or breastfeeding, you will not be allowed to participate in this study as there are a lot of risks that might be associated with harms for the pregnant women and the fetus. If you become pregnant or feel that you might be pregnant during the study, please contact your provider and study investigator.

**Fasting.**
You may have feelings of discomfort associated with skipping a meal (i.e. breakfast) including being hungry, stomach cramps, and stomach noises.

**MANAGING RISKS**
You will be routinely asked if you are experiencing any adverse effects from the study drink on the treatment days.

**Minor adverse effects.** In the event of minor adverse effects, the investigator will assist you in determining if you need further medical attention or the investigator can direct you to seek medical care at the emergency department, if necessary. You will also be given the investigator’s contact number to contact during normal business hours, to discuss about the side effects, if needed.

**Serious adverse effects.** In the event of a serious adverse effect, you will be instructed to call 9-1-1 or go to the closest emergency department. Alternatively, the investigator may call 9-1-1 too. You will be asked to notify the study investigators of any serious adverse effects, hospitalizations and ER/urgent care visits. If the serious adverse effect occurs while with the research team during treatment days, then you will be escorted to the nearest emergency room. After consulting with emergency department, you may be un-blinded or terminated from the study.

**PAYMENT FOR PARTICIPATION**
As compensation for participation, you will receive a $50 gift card at the end of the day 14 visit and a $50 gift card at the end of the day 28 visit, totaling to $100 at the completion of the full study. Withdrawal from the study before day 14 or day 28 would result in no compensation for that timeframe. Since you are receiving a gift card for your participation in this study, your name must be released to the University of the Pacific Finance Center for accounting purposes. To insure your confidentiality, your name will not be linked with this research study. Your name will only be linked with the fact that you received a gift card for research participation.

**CONTACT INFORMATION**
If you have any questions about the research at any time, please call May Chen at 209-932-2959 or 209-662-0786. If you have any questions about your rights as a participant in a research project please call the Office of Research & Sponsored Programs, University of the Pacific: (209) 946-7716. In the event of a research-related injury, please contact your regular medical provider and bill through your normal insurance carrier, then contact the Office of Research & Sponsored Programs. The University or the investigator will not bear any costs in case of any adverse effects. You will be responsible for all costs.
PRIVACY AND CONFIDENTIALITY
Any information that is obtained through this study and that can be identified with you will remain confidential and will be disclosed only with your permission. Measures to ensure your confidentiality include maintaining records in a locked cabinet or a password protected computer with access only available to the investigators. Collected data will also be de-identified before analyses by the investigators occur. Data will not be transmitted or copied to other hard drives or databases. After three years from the date of the study’s conclusion, the data will be destroyed. While we may publish or present the findings of the study, no personal information will be disclosed.

Your signature below indicates that you have read and understand the information provided above, that your participation is completely voluntary, that you may withdraw your consent and discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled, that you will receive a copy of this form, and that you are not waiving any legal claims, rights or remedies.

You will be provided a copy of this signed form to keep.

Signature                                         Print Name                                         Date

Study Participant

Signature                                         Print Name                                         Date

Primary Investigator

Signature                                         Print Name                                         Date

Witness