Acute effects of *Red Bull* energy drink on ventricular repolarization in healthy young volunteers: a prospective study

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ABSTRACT

Objective: Energy drinks (EDs) are widely consumed products of the beverage industry and are often chosen by teenagers and young adults. Several adverse cardiovascular events and malignant cardiac arrhythmias following consumption of EDs have been reported in the literature. Several studies have suggested that the interval from the peak to the end of the electrocardiographic T wave (Tp-e) may correspond to the dispersion of repolarization and that an increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. This study investigated the acute effects of *Red Bull* ED on ventricular repolarization as assessed by the Tp-e interval and Tp-e/QT ratio.

Methods: A prospective, open-label study design was used. After an 8-h fast, 50 young, healthy subjects consumed 355 mL of *Red Bull* ED. The Tp-e interval, Tp-e/QTc ratio, and several other electrocardiographic parameters were measured at baseline and 2 h after ingestion of *Red Bull* ED.

Results: No significant changes in the Tp-e interval or Tp-e/QTc ratio were observed with *Red Bull* ED consumption. *Red Bull* ED consumption led to increases in both systolic and diastolic blood pressures, which were associated with an increased heart rate.

Conclusion: Although ingestion of *Red Bull* ED increases the heart rate and diastolic and systolic blood pressures, it does not cause alterations in ventricular repolarization as assessed by the Tp-e interval and Tp-e/QTc ratio. *(Anatol J Cardiol 2015; 15: 919-22)*

Keywords: energy drink, adverse effect, blood pressure, ventricular repolarization, caffeine

Introduction

After multivitamins, energy drinks (EDs) are the most popular dietary supplements in the young adult population (1). EDs constitute a category of sugary drinks that contain variable amounts of caffeine, taurine, glucuronolactone, and other ingredients that may include vitamins and minerals (2). Despite their popularity, there are health concerns about EDs because of reported side effects such as cardiovascular complications. Previous case reports have linked EDs with sudden cardiac death, coronary vasospasm, reversible postural tachycardia syndrome, and serious arrhythmias including ventricular fibrillation (3). Many reports of adverse events linked to ED consumption have been listed in the Federal Drug Administration's recently released report on EDs, including 18 deaths and 1 nonfatal myocardial infarction (4).

Most adverse effects and toxicities associated with EDs have been attributed to the high caffeine content of EDs (5). Caffeine is a potent stimulant, particularly at high doses (6). Caffeine binds to the G-protein-coupled receptors on the surface of cardiac myocytes, ultimately leading to increases in intracellular cyclic AMP and calcium concentrations, mimicking the chronotropic and inotropic effects of adrenaline. Numerous clinical studies have shown that caffeine induces a temporary elevation in blood pressure and a slight reduction in heart rate (7, 8). EDs also contains high doses of taurine and glucuronolactone. Taurine can have deleterious effects on sodium channels and can cause arrhythmias (9). In addition, a recent study demonstrated that a single dose of a dietary supplement containing ephedra and caffeine resulted in significant prolongation of the QTc interval and P-wave duration, which are risk factors for the development of ventricular and atrial arrhythmias, respectively (10). EDs have also been shown to increase platelet aggregation (11), worsen endothelial function (11), reduce myocardial blood flow when consumed before exercise (12), and significantly increase oxygen demand (13).

Recent studies have shown that the length of the terminal part of the QT interval, defined as the distance between the peak and end of the T wave (Tp-e), is an index of the total spatial

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dispersion of cardiac repolarization (14). The Tp-e/QT ratio and the Tp-e/QTc ratio are also used as electrocardiographic indices of ventricular arrhythmogenesis (15). To the best of our knowledge, the effect of EDs on the Tp-e/QT and Tp-e/QTc ratios has not been determined. This study investigated the acute effects of *Red Bull* ED on several commonly used electrocardiographic parameters and ventricular repolarization as assessed by the Tp-e interval and Tp-e/QT ratio in healthy young subjects.

Methods

Study population

The study group comprised 52 healthy young students of Istanbul School of Medicine (mean age: 25±2.3 years). A prospective, open-label study design was used. All subjects had an unremarkable medical history and normal findings on physical examination, electrocardiography, and echocardiography. No subjects were taking any drugs, and no subjects were smokers. Two subjects were usual consumers of EDs (no more than 1 ED per week). Only 5 practiced sports. The characteristics of the study population are reported in Table 1.

Written informed consent was obtained from each subject, and the institutional Ethics Committee approved the study protocol.

Study design

All participants abstained from caffeinated products for at least 2 days before study initiation. All experiments took place in a quiet, temperature-controlled (20°C–22°C) laboratory and started between 8:00 am and 9:00 am. After an 8-h fast, all 50 subjects consumed 355 mL of *Red Bull* ED containing caffeine (114 mg), taurine (1.42 mg), glucuronolactone (84.2 mg), and sucrose and glucose (39.1 g) at room temperature. Baseline 12-lead electrocardiography was performed, and a subsequent 12-lead electrocardiography was performed 1 h and 2 h after ingestion of *Red Bull* ED.

Electrocardiogram and Tp-e interval measurement

All standard 12-lead electrocardiogram (ECGs) were recorded on digitized 12-lead ECG recordings using the on-screen digital caliper software Cardio Calipers version 3.3 (Iconico, Inc., New York, NY). Twelve-lead electrocardiography was performed before and 1 h and 2 h after consuming the ED. Lead V5 was selected in all ECG recordings for general comparisons of the PR, QRS, QT, and RR intervals.

The Tp-e interval was measured using the tangent method (13). The time (in ms) from the peak of the T wave (or nadir if a negative or biphasic T wave was obtained) and the intersection between the tangent at the steepest point of the T-wave downslope and the isoelectric line was measured. Because previous studies have postulated that precordial leads best reflect transmural dispersion of repolarization and that limb leads best reflect apical-basal or global spatial dispersion, the Tp-e interval was measured from the peak of the T wave to the end of the T wave using the best available T wave in lead V5, a method that has been described previously (14). When V5 was not suitable for analysis leads, V4 and V6 were measured. We used HR-corrected QT and Tp-e using Bazett's formula that has been used previously in HR correction ($n=n/\sqrt{RR}$). Subjects with U waves on their ECGs were excluded from the study. Two subjects had U waves and their T-wave amplitude was <1.5 mV on their ECGs and were excluded from the study.

Table 1. Baseline characteristics of the study population

	Study population (n=50) Mean±SD
Age, years	25±2.3
Male sex, %	30 (60%)
Weight, kg	74.69±6.10
Height, cm	170.4±4.89
BMI, kg/m^2	25.6±1.47
LVEF, %	65.25±6.96
LA diameter, mm	33.1±3
LVEDV/BSA, mL/m^2	85.4±9.82
LVESV/BSA, mL/m^2	35.7±11.4
IVSD, mm	8.22±0.55
Total cholesterol, mg/dL	171.67±39.61
Glucose, mg/dL	94±6.2
Hemoglobin, g/dL	14.1±2.37
Creatinine, mg/dL	1.1±0.32
BUN, mg/dL	15.2±5.8

BMI - body mass index; BSA - body surface area; LA - left atrium; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic diameter; IVSD - interventricular septum diameter

Statistical analyses

All statistical tests were conducted using the Statistical Package for Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Continuous data are expressed as means±standard deviation and categorical data as percentages. The paired sample t-test was used to assess differences between variables before and after *Red Bull* ED consumption. Statistical significance was assumed to be present at a 2-sided p value of <0.05.

Results

All 50 volunteers successfully completed the study. The subjects' baseline characteristics are shown in Table 1. ED did not significantly alter the PR, QRS, QT, QTc, Tp-e, and cTp-e intervals and the Tp-e/QT and Tp-e/QTc ratios compared with baseline (Table 2, 3). However, systolic blood pressure (SBP) increased from 112±6.1 mm Hg at baseline to 123±6.9 mm Hg after 1 h (p=0.003) and 121±7.4 mm Hg after 2 h (p=0.006); diastolic blood pressure (DBP) increased from 73±5.3 mm Hg at baseline to 77.4±6.4 mm Hg after 1 h (p=0.05) and 76.3±6.2 mm Hg after 2 h (p=0.008). The heart rate increased from 77.96±14.94 beats/min at baseline to 83.8±12.1 beats/min after 1 h (p=0.008) and 84.8±10.7 beats/min after 2 h (p=0.005). There was no difference in these parameters between males and females. The interobserver and intraobserver coefficients of variation were 2.5% and 2.8%, respectively.

Table 2. Heart rate and electrocardiographic and blood pressure parameters before and after 1 h of energy drink (ED) consumption

	Before ED Mean±SD (n=50)	After 1 h of ED consumption Mean±SD (n=50)	*P*
Heart rate, bmp	77.96±14.94	83.8±12.1	0.008
Systolic BP, mm Hg	112±6.1	123±6.9	0.003
Diastolic BP, mm Hg	73±5.3	77.4±6.4	0.005
PR interval, ms	167.2±26.1	170±26.3	0.9
QRS duration, ms	90.5±9.7	94±10.4	0.7
QT interval, ms	384.1±14.3	387±12.6	0.37
QTc interval, ms	406.4±20.6	418±23.4	0.3
Tp-e, ms	67.3±15.9	69.2±15.8	0.44
cTp-e, ms	69.3±16.8	72±15.2	0.5
Tp-e/QT	0.17±0.03	0.18±0.04	0.47
Tp-e/QTc	0.16±0.02	0.17±0.02	0.41

BP - blood pressure; bmp - beats/minute; ms - milliseconds; Tp-e - distance between the peak and the end of the T wave

Table 3. Heart rate and electrocardiographic and blood pressure parameters before and after 2 h of energy drink (ED) consumption

	Before ED Mean±SD (n=50)	After 2 h ED Mean±SD (n=50)	*P*
Heart rate, bmp	77.96±14.94	84.8±10.7	0.005
Systolic BP, mm Hg	112±6.1	121±7.4	0.006
Diastolic BP, mm Hg	73±5.3	76.3±6.2	0.008
PR interval, ms	167.2±26.1	171±28.5	0.71
QRS duration, ms	90.5±9.7	94±11.1	0.7
QT interval, ms	384.1±14.3	386±11.6	0.37
QTc interval, ms	406.4±20.6	417.4±24.7	0.34
Tp-e, ms	67.3±15.9	68.8±16.1	0.5
cTp-e, ms	69.3±16.8	71.2±15.9	0.53
Tp-e/QT	0.17±0.03	0.18±0.02	0.45
Tp-e/QTc	0.16±0.02	0.17±0.03	0.36

BP - blood pressure; bmp - beats/minute; ms - milliseconds; Tp-e - distance between the peak and the end of the T wave

Discussion

In this study, single low-dose *Red Bull* ED consumption did not acutely affect ventricular repolarization as assessed using the Tp-e and cTp-e intervals and the Tp-e/QTc ratio. It also did not affect other conventional electrocardiographic parameters, such as the PR, QRS, QT, and QTc intervals. The heart rate and mean SBP and DBP increased 1-2 h after ED ingestion.

"Energy drinks" are beverages that contain caffeine, taurine, vitamins, herbal supplements, and sugar or sweeteners, and they are marketed to improve energy, weight loss, stamina, athletic performance, and concentration (16). EDs contain 3-4-fold the amount of caffeine in a typical soda and may boost performance and enhance metabolism. Caffeine is a well-known and commonly used neurostimulant. The mechanism of action is believed to be direct adenosine receptor stimulation in addition to the effects on monoamine neurotransmitters. Caffeine is a potent stimulant, particularly at high doses (17, 18). It binds to the G-protein-coupled receptors on the surface of cardiac myocytes, ultimately leading to a rise in intracellular cyclic AMP and calcium concentrations, mimicking the chronotropic and inotropic effects of adrenaline (18, 19). Caffeine may also enhance the inotropic effect of β-adrenergic agents. It has been shown to directly stimulate cardiac function while dilating blood vessels and appears to increase blood pressure in humans (7, 8). Documented adverse cardiovascular effects include tachycardia, extrasystoles, increased stroke volume, and possibly other arrhythmias (3, 20). In some cases, caffeine is believed to precipitate serious adverse events such as myocardial infarction and cardiac arrest. In addition, EDs contain high doses of taurine, inositol, and glucuronolactone. High doses of taurine shorten the duration of the action potential and decelerate the rate of terminal repolarization of the cardiac action potential, promoting atrial and ventricular arrhythmias or cardiac arrest (15, 21).

Previous studies have evaluated changes in electrocardiographic variables after caffeine consumption. Ammar et al. (22) observed that moderate caffeine consumption by healthy young adults does not affect the PR, QRS, QT, QTc, or RR intervals or the QT or QTc interval dispersion. The effect of caffeine (1 mg/kg of body weight) on the cardiac rhythm was investigated by Sutherland et al. (23) who reported no QT interval prolongation. Steinke et al. (24) determined the cardiac effects of 500 mL of ED daily (80 mg of caffeine) in 15 healthy volunteers and found no significant electrocardiographic changes. In accordance with previous studies, we found that consumption of *Red Bull* ED did not alter the PR, QRS, QT, or QTc intervals. In addition, we investigated ventricular repolarization using the Tp-e interval and Tp-e/QTc ratio. Many studies have reported that an increased dispersion of repolarization may result in predisposition to the development of ventricular arrhythmias. Siciouri et al. (25) reported an association between ventricular arrhythmias and the Tp-e interval. The duration of the action potential is longer in the middle myocardial M cells than in other myocardial cells. The peak of the T wave represents the end of the epicardial action potential, and the end of the T wave represents the end of the mid-myocardial action potential. Therefore, the Tp-e interval is a reflection of the dispersion of repolarization and can be helpful in predicting the risk of development of life-threatening arrhythmias (13). Evidence in support of this hypothesis has been provided by studies of patients with hypertrophic cardiomyopathy (26), long QT syndrome (27), Brugada syndrome (28), and other pathophysiological conditions. We evaluated the acute effects of ED consumption on the Tp-e interval and Tp-e/QT ratio and found no significant changes in either. In light of these limited results, EDs do not appear to have a significant unfavorable acute influence on left ventricular repolarization at low doses. Sovaca et al. (29, 30) performed 2 prospective studies and demonstrated that caffeine intake is significantly correlated with elevated daytime SBP and DBP. In accordance with these

results, we found that SBP, DBP, and heart rate were significantly increased after *Red Bull* ED consumption.

Study limitations

This study was limited by the relatively small number of subjects. We evaluated only the effects of low-dose ED consumption. At higher doses, the results may be different. The Tp-e measurement method may have influenced our results. Conducting more frequent blood pressure measurements and serial ECGs to identify the timing of the greatest change in blood pressure and each electrocardiographic parameter may provide additional insights. Furthermore, our results are limited to healthy subjects and require confirmation in other more vulnerable cohorts, such as those with cardiovascular risk factors.

Conclusion

We conclude that although *Red Bull* ED acutely increases the heart rate, SBP, and DBP, it does not appear to have a significant unfavorable acute influence on left ventricular repolarization as assessed by the Tp-e interval and Tp-e/QTc ratio at low doses. Further studies should aim to identify possible cardiovascular effects of EDs at higher doses.

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