



Cardiovascular Effects of Energy Drinks in Familial Long QT Syndrome: A Randomized Cross-Over Study



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ABSTRACT

Background: Caffeinated energy drinks may trigger serious cardiac effects. The aim of this study was to determine the cardiovascular effects of caffeinated energy drink consumption in patients with familial long QT syndrome (LQTS).

Methods and Results: From 2014–2016, 24 LQTS patients aged 16–50 years were recruited to a randomized, double-blind, cross-over study of energy drink (ED) versus control (CD) with participants acting as their own controls (one week washout). The primary study outcome was an increase in corrected QT interval (QTc) by >20ms. Secondary outcomes were changes in systolic and diastolic blood pressure.

In 24 patients with LQTS (no dropout), mean age was 29 ± 9 years, 13/24 (54%) were female, and 8/24 (33%) were probands. Intention to treat analysis revealed no significant change in QTc with ED compared with CD (12 ± 28 ms vs 16 ± 27 ms, 3% vs 4%, $p = 0.71$). The systolic and diastolic blood pressure significantly increased with ED compared to CD (peak change 7 ± 16 mmHg vs 1 ± 16 mmHg, 6% vs 0.8%, $p = 0.046$ and 8 ± 10 vs 2 ± 9 mmHg, 11% vs 3% $p = 0.01$ respectively). These changes correlated with significant increases in serum caffeine (14.6 ± 11.3 vs 0.5 ± 0.1 $\mu\text{mol/L}$, $p < 0.001$) and serum taurine (737 ± 199 vs -59 ± 22 $\mu\text{mol/L}$, $p < 0.001$). There were three patients with dangerous QTc prolongation of ≥ 50 ms following energy drink consumption.

Conclusion: Caffeinated energy drinks have significant haemodynamic effects in patients with LQTS, especially an acute increase in blood pressure. Since dangerous QTc prolongation was seen in some LQTS patients, we recommend caution in young patients with LQTS consuming energy drinks.

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1. Introduction

Caffeinated energy drinks may cause life-threatening arrhythmias amongst individuals with no previous history of heart disease [1–3], and can unmask an underlying primary arrhythmogenic disease such as familial long QT syndrome (LQTS) [4–7]. The haemodynamic effects of energy drinks in healthy young adults has been previously assessed with varying results, including increased blood pressure, but no change in heart rate [8–10]. Energy drinks may have specific adverse cardiovas-

cular effects in patients with primary arrhythmogenic diseases, including risk of arrhythmias and other haemodynamic effects, especially in those exacerbated by adrenergic stimulation such as in LQTS.

Few studies have systematically assessed the cardiovascular effects of caffeinated energy drinks in higher risk disease populations. This study sought to assess the acute cardiovascular responses to energy drink consumption in patients with LQTS compared to placebo control, and to determine whether any identified cardiovascular effects correlate with changes in blood levels of the active ingredients, caffeine and taurine.

2. Methods

2.1. Patient Selection

LQTS patients aged 16–50 years were recruited between 2014 and 2016 from the Genetic Heart Disease Clinic at Royal Prince Alfred Hospital, Sydney Australia, and the Australian Genetic Heart Disease

Abbreviations: LQTS, long QT syndrome; QTc, corrected QT interval; ED, energy drink; CD, control drink; ECG, electrocardiogram.

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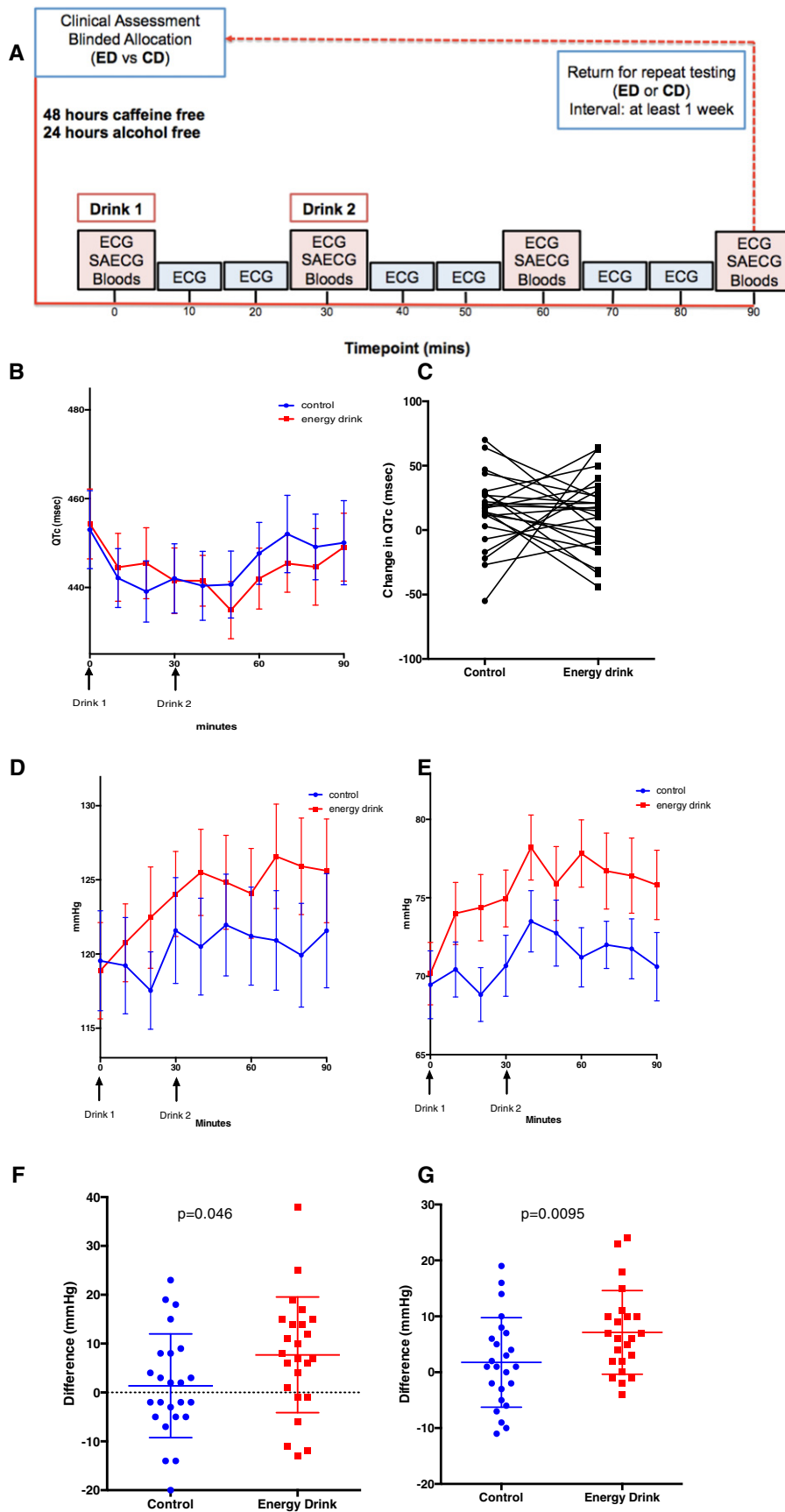


Fig. 1. (A) Study Protocol: Randomized, double-blind, cross-over study with participants acting as their own controls (one week washout period). Participants received two doses of drinks at zero and 30 min and were observed for a total of 90 min. Comparison between energy drink and control drink: overall (B) QTc and (C) maximum change in QTc; overall (D) systolic and (E) diastolic blood pressure changes during the study; peak (F) systolic and (G) diastolic blood pressure changes (paired *t*-test). Results shown as mean \pm SEM. ED - energy drink, CD - control drink, ECG - electrocardiogram, SAEKG - signal averaged ECG, Bloods - caffeine and taurine levels

Table 1
Cohort Baseline characteristics.

Characteristic	Value n (%)
Age (years)	29 ± 9
Male sex	11 (46)
Proband	8 (33)
History of syncope	13 (54)
Implantable cardioverter-defibrillator (ICD) therapy	10 (42)
Aborted cardiac arrest or appropriate ICD shock	4 (17)
Family history of sudden cardiac death	12 (50)
Beta-blocker therapy	20 (83)
• propranolol	4
• atenolol	9
• metoprolol	7
Schwartz Score (diagnostic if ≥3.5)	4.3 ± 1.1
Genetic testing performed	20 (83)
Likely pathogenic or pathogenic variant	
<i>KCNQ1</i> (LQT1)	3 (15)
<i>KCNH2</i> (LQT2)	10 (50)
<i>SCN5A</i> (LQT3)	0 (0)
Typical daily caffeinated drink intake	
0	2 (8)
1	10 (42)
2	4 (17)
> 2	8 (33)

Registry [11]. The diagnosis of LQTS was confirmed through established diagnostic criteria [12]. *A priori* sample size calculations (see below) indicated 24 patients would be required. Eighty-four patients were

eligible for the study of whom 49 were geographically located to present for two 90-min study visits. Participants were approached until the sample size was reached (**Supplementary data**). Study participants provided written consent, received no financial stipend, and all studies were conducted in strict accordance with the Sydney Local Health District Ethics Review Committee.

2.2. Study Protocol

The study protocol is shown in Fig. 1A. Participants were instructed to be caffeine-free for 48hr prior to the study and alcohol-free for 24hr. Participants were then randomized to energy drink (ED) or control drink (CD) for the first study visit. The investigators were blinded to the allocation of the drinks which were prepared as follows in identical opaque bottles by an independent research assistant.

- **ED:** 2 x Red Bull Sugar-free cans = TOTAL 160mg caffeine + 2000mg taurine in 500mL OR
- **CD:** 2 x control drink (cordial-based), no caffeine or taurine in 500mL.

Baseline clinical assessment included basic demographic information, history, physical examination, usual daily caffeine intake, and any relevant genetic testing results. Standard 12-lead ECG and signal averaged ECG (SAECG) were recorded and baseline blood tests performed (serum caffeine & taurine levels).

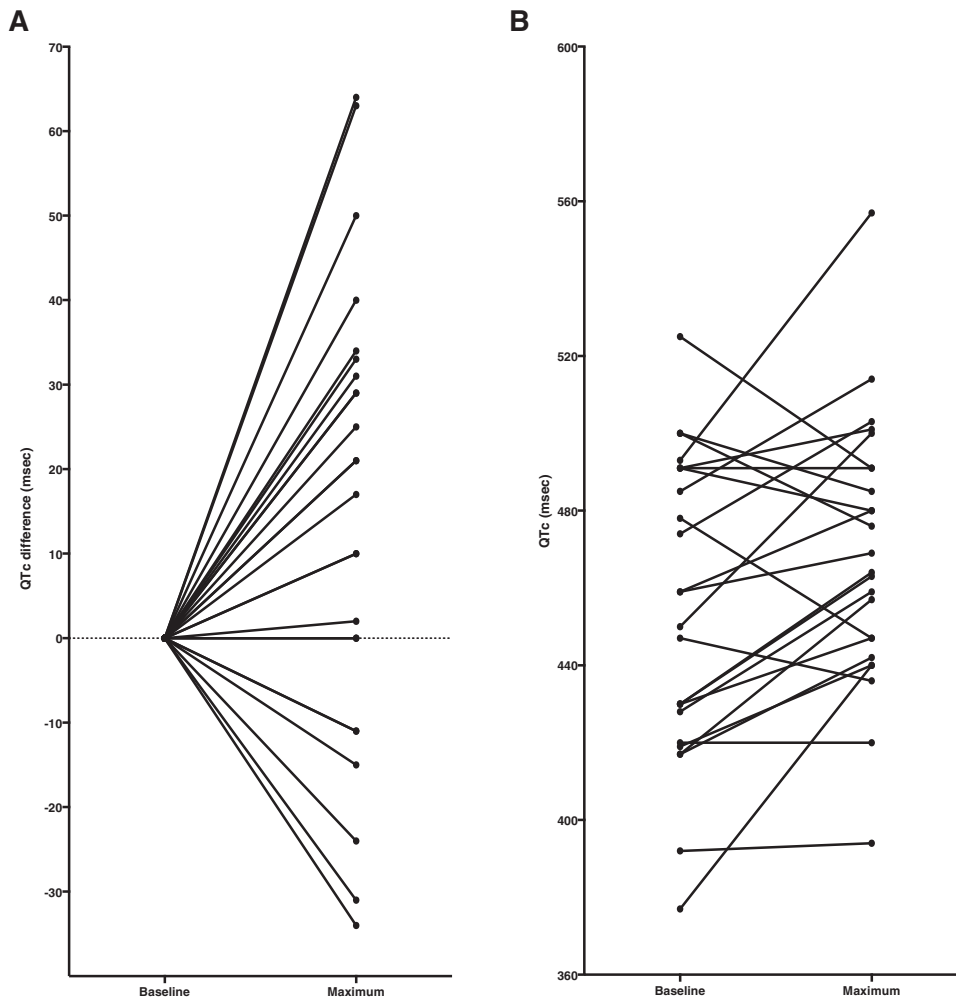


Fig. 2. Changes in QTc following energy drink consumption (**A**) difference in QTc and (**B**) overall raw QTc changes from patient's baseline value.

Table 2

Phenotype of 3 patients with significant QTc prolongation following ED consumption.*

Patient Code	Age/Sex	QTc at diagnosis (ms)	Genetic Testing	LQTS genotype	Symptoms	Schwartz Score	Family history of SCD	Betablocker therapy	HR pre/post (bpm)	QTc pre/post (ms)
2	27/F	550	Yes	indeterminate	Syncope + ICD shock	5	Yes	Propranolol	45 51	493 557
4	24/M	510*	Yes	indeterminate	No	4	Yes	Metoprolol	46 46	380 440
14	46/M	480	Yes	LQT2	Syncope	5	Yes	Metoprolol	50 63	450 500

Table Legend: ms- milliseconds, SCD- sudden cardiac death, HR- heart rate, QTc- corrected QT interval, pre/post- baseline and maximum change with energy drink.

* Patient 4 was diagnosed on family screening in 2011 with QTc = 510 ms occurring both in recovery of exercise stress testing and following epinephrine challenge (Mayo clinic protocol).

Participants were administered the drinks at zero and 30 min time points. Serial ECGs and blood pressures were recorded every 10 min, whilst SAECG and repeat bloods were collected every 30 min for a total observation time of 90 min. Patients acted as their own controls and returned for alternative drink after at least 1 week washout. The QT measurements were performed by two independent blinded cardiologists (BG/CM) and corrected using Bazett's formula ($QTc = QT/\sqrt{RR}$).

2.3. Statistical Analysis

Intention to treat statistical analyses were carried out using IBM SPSS Statistics (Version 23) and GraphPad Prism 6. Continuous variables were assessed between the two groups using two-sample paired *t*-tests. Categorical variables were compared using chi-square and Fisher's exact tests. Significance was set at a two-sided *p* value of 0.05.

2.4. Power Calculations

The primary aim of the study was to assess a continuous response variable (prolongation in QTc interval) from matched pairs of study subjects (whereby patient acts as their own control). Following ethics approval for this study, we performed a small pilot study in 9 control (healthy volunteers) subjects to ensure feasibility of the proposed study methods. Data from the feasibility study indicated that the difference in the response of matched pairs is normally distributed with standard deviation 30 ms. If the true difference in the mean response of matched pairs is a prolongation in QTc interval of >20 ms and the standard deviation is the same as the normal population, we estimated we needed a minimum of 24 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with power of 90% and type I error probability of 0.05.

3. Results

3.1. Baseline cohort characteristics

All twenty-four LQTS patients completed both arms of the study, with no dropout. The baseline characteristics are shown in Table 1. The mean age was 29 ± 9 years, 33% were probands, and 54% were

female. The mean Schwartz score was 4.3 ± 1.1 [13]. Most patients were symptomatic prior to diagnosis (58%) and were receiving beta-blocker therapy (83%). Most had undergone genetic testing (83%) of whom 13 (65%) had a documented *pathogenic* or *likely pathogenic* mutation in *KCNQ1* and *KCNH2*. Most patients (67%) had a daily caffeine intake of ≤ 2 drinks.

3.2. Electrocardiographic and arrhythmic effects of energy drink consumption

The study protocol is shown in Fig. 1A. Baseline QTc between the two study days were not different [453 ± 43 ms (CD) vs 454 ± 39 ms (ED), $p = 0.81$]. The proportion of patients who demonstrated a change in QTc of ≥ 20 ms (primary outcome) was not different between the two groups (8/24, 33% vs 9/24, 38%, $p = 1.0$). The overall change in QTc was not different between CD and ED (maximum change 12 ± 28 ms vs 16 ± 27 ms, 3% vs 4%, $p = 0.71$; Fig. 1B and C). The difference in QTc from zero and absolute QTc change from baseline following ED consumption is shown in Fig. 2. Three patients had an increase in QTc of ≥ 50 ms after consumption of ED, all with a documented family history of sudden cardiac death (details in Table 2; Fig. 3).

The average baseline heart rate was not different between the ED and CD groups, with no significant changes in overall heart rate throughout the study (mean change -7% for both groups, $p = 0.94$). There were no patients with documented ventricular arrhythmias, significant symptoms or development of late potentials on SAECG during the study.

3.3. Haemodynamic effects of energy drink consumption

Mean baseline systolic and diastolic blood pressures were within normal limits and similar on the two study days (ED 119/70 mmHg vs CD 120/70 mmHg). The overall change in systolic and diastolic blood pressure is shown in Fig. 1D and E. The maximum change in systolic blood pressure was seen at 70 min (7 ± 16 mmHg vs 1 ± 16 mmHg, 6% vs 0.8% $p = 0.046$) and in diastolic blood pressure at 60 min (8 ± 10 vs 2 ± 9 mmHg, 11% vs 3%, $p = 0.01$; Fig. 1F and G). These blood pressure changes correlated with significant increases in serum caffeine

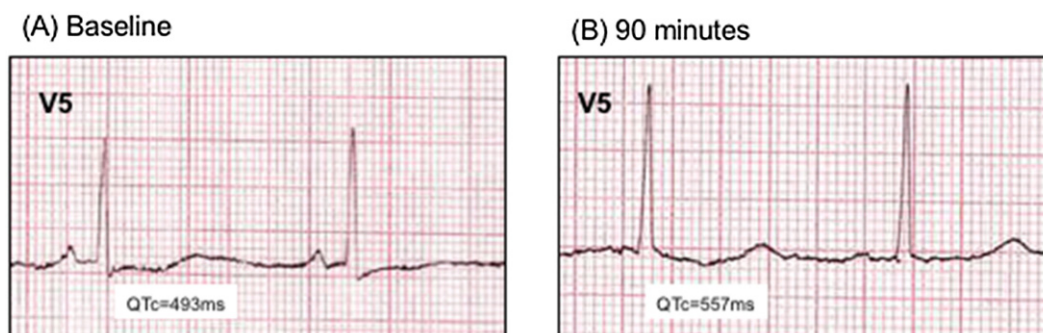


Fig. 3. Patient 2 ECG at baseline (A) and 90 min (B) after ED showing QTc prolongation of 60 ms.

(26 ± 8 vs 0 ± 1 $\mu\text{mol/L}$, $p < 0.001$) and serum taurine (737 ± 199 vs -59 ± 22 $\mu\text{mol/L}$, $p < 0.001$).

4. Discussion

The potential cardiovascular risk of energy drinks continues to emerge as an important public health issue [10,14]. The population most at risk are teenagers and young adults, representing the population these drinks are most heavily marketed towards. Since energy drinks are widely available to all ages and over the counter, it is important that cardiovascular effects of these drinks are investigated. Several case reports of individuals experiencing adverse events including serious life-threatening arrhythmias and cardiac arrest following consumption of energy drinks have been reported [1–6]. The findings of the current study identify additional acute haemodynamic responses to consumption of energy drinks. Our findings are similar to those recently described by Svatikova et al. in a normal population [10]. The significant increase in blood pressure was similar when comparing both studies, as was the absence of changes in heart rate. Such acute elevations in blood pressure can provide a substrate for adverse cardiovascular events, including stroke [15].

Our study differs from prior investigations of cardiovascular effects of energy drinks as the focus was on patients with familial LQTS who are at an increased risk of arrhythmias and other adverse cardiovascular events compared to a normal population [16]. Whilst the overall changes in QTc, the main ECG-based indicator of LQTS severity, were not significant between the ED and CD groups, there were interesting individual responses with clinical relevance. Three LQTS patients had a clinically relevant QTc increase of at least 50 ms after consumption of energy drink (Table 2, Fig. 3). These patients all had a documented family history of sudden cardiac death; two of the three patients were known to have a severe phenotype with resting QTc > 500 ms and had an implantable cardioverter-defibrillator for recurrent syncope. These “case studies” within our study cohort highlight the potential cardiac effects of at-risk, individual patients consuming energy drinks, particularly in those with a more severe phenotype.

4.1. Limitations

Several factors may have limited the extent of cardiovascular effects in this unique patient cohort. In order to ensure safety, there were some elements of the study design which potentially limited the effects of the drinks: firstly, the doses of energy drinks administered may not have been sufficient to induce significant effects on the QTc interval or to induce arrhythmias. Similarly, repetitive doses over a longer time frame (>90 min) may have led to more significant effects. Due to ethical considerations, LQTS patients continued their beta-blocker therapy during the study which may have reduced the magnitude of the blood pressure response, and protected against arrhythmias. Further, the LQTS cohort was overall clinically mild, with a mean baseline QTc of 454 ms, and therefore a study in more clinically severe LQTS may have more significant cardiovascular effects.

5. Conclusions

Caffeinated energy drinks have significant haemodynamic effects in patients with familial LQTS compared to placebo control, specifically an acute increase in blood pressure. While there was no significant effect on QTc interval, there were some individual patients who may be at a higher risk with dangerous QTc prolongation evident in some LQTS

patients. We suggest caution in allowing the consumption of energy drinks in young patients with LQTS.

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Conflicts

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.12.019>.

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