Energy Drinks Induce Acute Cardiovascular and Metabolic Changes Pointing to Potential Risks for Young Adults: A Randomized Controlled Trial

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ABSTRACT

Background: Case reports suggest a link between energy drinks (EDs) and adverse events, including deaths.

Objectives: We examined cardiovascular and metabolic effects of EDs and mixtures providing relevant ingredients of EDs compared to a similarly composed control product (CP) without these components.

Methods: This randomized, crossover trial comprised 38 adults (19 women, mean BMI 23 kg/m², mean age 22 y). We examined effects of a single administration of a commercial ED, the CP, and the CP supplemented with major ED-ingredients at the same concentrations as in the ED. The study products were administered at 2 volumes, 750 or 1000 mL.

Results: Both volumes of the study products were acceptably tolerated with no dose-dependent effects on blood pressure (BP, primary outcome), heart rate, heart rate corrected duration of QT-segment in electrocardiography (QTc interval), and glucose metabolism. After ED consumption, 11% of the participants reported symptoms, in contrast to 0–3% caused by other study products. After 1 h, administration of an ED caused an increase in systolic BP (116.9 ± 10.4 to 120.7 ± 10.7 mmHg, mean ± SD, P < 0.01) and a QTc prolongation (393.3 ± 20.6 to 400.8 ± 24.1 ms, P < 0.01). Also caffeine, but not taurine or glucuronolactone, caused an increase in BP, but no QTc prolongation. The BP effects were most pronounced after 1 h and returned to normal after a few hours. All study products caused a decrease in serum glucose and an increase in insulin concentrations after 1 h compared to baseline values, corresponding to an elevation in the HOMA-IR (ED + 4.0, other products + 1.0–2.8, all P < 0.001).

Conclusion: A single high-volume intake of ED caused adverse changes in BP, QTc, and insulin sensitivity in young, healthy individuals. These effects of EDs cannot be easily attributed to the single components caffeine, taurine, or glucuronolactone. This trial was registered at clinicaltrials.gov as NCT01421979. J Nutr 2019;149:1–10.

Keywords: energy drinks, caffeine, taurine, glucuronolactone, cardiovascular risk, hypertension, QTc interval, glucose tolerance, young adults

Introduction

Energy drinks (EDs) are popular nonalcoholic beverages. The popularity of EDs has substantially increased globally since their introduction in the 1960s (1), and they are reported to be the fastest growing segment of the beverage industry (2). Most EDs are targeted towards young adults aged between 18 and 34 y (2), with a reported consumption frequency of 1–4 d/mo (3), especially on occasions such as visits to nightclubs, festivals, sports events, and gaming parties (2, 4). According to a German survey, individuals drink on average about 1 L (at maximum 4 L) of EDs during 1 d (3), often mixed with alcohol (2, 3, 5, 6). The German Federal Ministry of Food and Agriculture regulation on fruit juice (2012) defines EDs as refreshing drinks, which, besides caffeine, contain ≥1 more component such as taurine, inositol, or glucuronolactone (7). Besides these main components, other ingredients, for example, carbohydrates, electrolytes, vitamins, botanical extracts, food colors, and flavorings are found in EDs (2).

A number of case reports have documented acute adverse effects, including fatalities, in individuals consuming EDs with or without alcohol at mostly, but not always, high amounts (5, 8–10). The principal symptoms observed after ED consumption were essentially cardiovascular [e.g., chest
tightly or pain, tachycardia, high blood pressure (BP), and arrhythmia even leading to cardiac arrest], gastrointestinal, or neurological (e.g., irritability, nervousness, anxiety and panic attacks, hallucinations, and epileptic seizures) (8).

Physiological and pharmacological effects of the main components of EDs, caffeine, taurine, inositol, and glucuronolactone, and other ingredients such as vitamins, have been reported (2, 11–21), and for some, adverse or toxic effects are known (11, 17, 22–27). However, it remains unclear which of these components or combinations contributes to the reported adverse effects related to ED consumption. Moreover, dose-dependent cardiovascular effects of single ED ingredients are still unknown. To the best of our knowledge, the high dose of these ingredients, as they would be found in the high volume of 1 L of ED, as commonly consumed nowadays, has not been used previously in a study setting.

Therefore, we first aimed to investigate the occurrence of adverse effects, besides cardiovascular and metabolic alterations, and occurring symptoms by administering a commercial ED, control product (CP), and 2 study products containing caffeine or taurine at 2 different volumes of 750 mL and 1000 mL, representing 3, respectively, 4 standard cans of 250 mL ED. Secondly, the present study aimed to compare the cardiovascular and metabolic effects of the ED with those of the CP, and of corresponding concentrations of the single components caffeine or taurine, a combination of caffeine and taurine, or glucuronolactone added to the CP at the higher volume of 1 L. The whole study setting served as a prior experimental setup to test safety and tolerance within a study population intended to be enrolled in a follow-up study in which the combined effects of ED and alcohol will be investigated (not shown here).

Participants and methods

Study population
Study participants were recruited by advertisement between May and October 2011 among university and vocational school students in Stuttgart, Germany. Eligible for the present study were young adults (aged 18–25 y), who responded to the advertisement (n = 55) and contacted the study center via phone or mail, followed by phone screening to check inclusion/exclusion criteria, that is, BMI between 20 and 25 kg/m2, no considerable habitual consumption of coffee (maximum 1 cup/d), alcohol (maximum 60 g/wk in males, 30 g/wk in females), or EDs (maximum 500 mL/wk). We included participants who reported regular leisure time exercise, and were neither sedentary nor athletes in regular physical training or competition. Exclusion criteria were regular medication intake (except contraceptives), a history of cardiovascular, metabolic, neurological, mental, or other medical disorder, a history of substance abuse, and pregnancy or lactation. Participants were instructed to abstain from nutritional supplements during the course of study. Forty-two out of 55 individuals met the inclusion criteria and were invited for a detailed medical examination. For the present study, we further excluded 4 participants because of doubtful medical history (n = 1) or refusal to provide written consent (n = 3), thus the final study population consisted of 38 participants (Figure 1). Participants gave their written informed consent and the study was approved by the Ethics Committee of the Medical Association of Baden-Württemberg (No. F-2011–020, May 5, 2011) and registered at clinicaltrials.gov (NCT01421979).

Study design
The study was conducted at the Metabolic Unit of the University of Hohenheim in Stuttgart, Germany. It was designed as a randomized, double-blind, controlled trial performed in a parallel and crossover manner. The study complied with the Helsinki Declaration as revised in 1983.

Volume-response.
Thirty-eight volunteers were randomly assigned to 2 parallel intervention groups, matched for sex and smoking status. One intervention group (n = 19) received a singular volume of 750 mL of the study products (G750), and the other (n = 19) received 1000 mL of the same study products (G1000) (Figure 1). In each group the study products were tested on 4 different days. Experimental days were separated by a washout phase of ≥4 d to ensure complete elimination of the study products. The study products comprised a commercial ED, CP, CP supplemented with taurine (CP + T), and CP supplemented with caffeine (CP + C). The order of administration of the study products was randomly assigned to each participant.

Effects of ED and its components on cardiovascular and metabolic parameters.
Because we had not noted any volume-dependent difference between G750 and G1000, and the latter volume was proven to be applicable in the study, participants of G1000 were invited to participate in an extended trial to further investigate 2 additional study products: CP supplemented with glucuronolactone (CP + G) and CP supplemented with a combination of caffeine and taurine (CP + C + T) at 1000 mL, in addition to the previous 4 study products. The 2 extended study products were tested on 2 different days, again with randomized order of administration. The 2 experimental days were also separated by a washout phase. Of the 19 already included individuals, 15 agreed to participate in this extended trial (Figure 1).

Interventions
Figure 2 depicts the collection of cardiovascular and metabolic parameters at 5 time points (TP) on each experimental day. Baseline data were collected in the morning, under fasting conditions, between 0800 and 0900 (TP0). This was followed by administration of the study product. The participants were instructed to consume 250 mL of study product within 15 min; therefore the administration required 45 min (G750) or 1 h (G1000). One hour after consumption, that is, 1.75–2 h after baseline, the data set TP1 was obtained (Figure 2). The TP0...
and TP1 data sets comprised blood sampling, cardiovascular parameters [BP, electrocardiography (ECG)], and symptom assessment (Figure 2). Three hours after consumption, the data set TP2 was collected, but without blood sampling (Figure 2). After collection of TP2, the participants were discharged. About 7 h (TP3) and 11 h (TP4) after consumption, participants recorded heart rate (HR) and BP at home (Figure 2). During each study day, heart rhythm was monitored by a 24-h-ECG-device.

Participants were instructed to avoid any food, beverages, and medications containing caffeine or alcohol for ≥72 h before each experimental day. Caffeine and glucose concentrations were monitored for compliance by measuring serum concentrations on the morning of each experimental day. Female

![Figure 1](https://academic.oup.com/jn/advance-article-abstract/doi/10.1093/jn/nxy303/5365182)

**FIGURE 1** Flow chart of patients enrolled in the study: 38 volunteers, randomly assigned to 2 parallel intervention groups, matched for sex and smoking status. First part: investigation of the volume response of 4 study products (CP, ED, CP + C, CP + T). Second part: investigation of singular or additive effects of CP, ED, CP + C, CP + T, CP + C + T, CP + G in G1000. Of the 19 already included individuals, 15 agreed to receive 2 additional study products (CP + C + T, CP + G). CP; control product; CP + C, control product with caffeine; CP + C + T, control product with caffeine and taurine; CP + G, control product with glucuronolactone; CP + T, control product with taurine; ED, energy drink; G750/G1000, study groups for test volumes 750 or 1000 mL.

![Figure 2](https://academic.oup.com/jn/advance-article-abstract/doi/10.1093/jn/nxy303/5365182)

**FIGURE 2** Procedures during 1 experimental day. Timeline of data collection at 5 time points at each experimental day. TP0 and TP1 data sets comprised blood sampling, blood pressure, electrocardiography, and symptom assessment. At TP2 blood pressure, electrocardiography, and symptoms were assessed. Blood pressure and symptoms were recorded at home 7 h and 11 h (TP3, TP4) after consumption heart rate. TP, time point.
participants underwent a urinary pregnancy test before each experimental set.

**Study products**
The present study was performed with the “Red Bull” ED, 3–4 cans of 250 mL (Red Bull GmbH), as we aimed to use a representative commercial product. The CP was the commercial sports drink “Xenofit Competition Citrus-Frucht” (Xenofit GmbH), which is available in soluble powder form. The CP was selected to match the nutritional constituents of the ED, but lacks the typical components of EDs, caffeine, taurine, inositol, and glucuronolactone. The single ED components were added to the CP at concentrations of 32 mg/100 mL caffeine, 400 mg/100 mL taurine, or 31 mg/100 mL glucuronolactone, or a combination of caffeine and taurine. These concentrations of caffeine, taurine, and glucuronolactone were selected for addition to the CP because they are identical to those in the Red Bull ED. Concentrations of caffeine and taurine were matched with the concentrations as given by the manufacturer of Red Bull ED, whereas the glucuronolactone content of the ED was measured by an accredited laboratory. Bottled lemon juice (10–20 mL/250 mL), raspberry syrup (30–80 mL/250 mL), and mineral water were added to all study products, which were served in white cups with lid and straw, for blinding purposes and to balance electrolyte and energy content of the different drinks. **Supplemental Table 1** provides detailed compositions of ingredients of each study product. All drinks were purchased in local supermarkets or via German online-retailers. Caffeine, taurine, and glucuronolactone were bought at a pharmacy.

**Outcome variables**
The primary outcome variable, BP, was measured using an automated system (R5 Professional, OMRON Healthcare Co.). Participants were instructed on how to perform a standardized measurement at home, to rule out confounding factors. Mean arterial pressure (MAP) was derived from systolic and diastolic measurement at home, to rule out confounding factors. Mean automated system (R5 Professional, OMRON Healthcare Co.).

**Sample size estimation**
The sample size was calculated, assuming a clinically relevant increase of systolic BP ≥7.5 mmHg after consumption of 1 of the study products compared to CP. Assuming a SD for systolic BP of 10 mmHg, a level of significance of 5%, and a power of 80%, 15 participants were required per group for the study. Accounting for a dropout rate of 20%, we aimed to enroll ≥18 participants (G∗power, t test for paired samples).

**Statistical analyses**
Data are reported as mean ± SD or median (IQR). Comparisons are presented by showing the data in the respective groups together with the P value of a post hoc t test.

Data were evaluated by fitting for each outcome variable (difference between TP0 and TP1 of serum caffeine, MAP, systolic BP, diastolic BP, QTc interval, and log-transformed HR, glucose, insulin, HOMA-IR, potassium) a nested series of linear mixed models, starting with a model containing a random subject effect and fixed effects for study product, volume, and treatment order. As the design was not fully balanced and each individual ordering was used at most twice, it was not feasible to include all period and carryover effects as a variable in the model. Instead, all pairwise orderings of the 4 initial treatments were included in the model. To obtain meaningful P values it is necessary to have normally distributed residuals. Using the Shapiro-Wilk test and QQ normality plots, we decided to log-transform the HR, glucose, insulin, HOMA-IR, and potassium. Ideally, none of the ordering effects will show a significant effect, indicating that the crossover design is valid and any interferences of having different treatments for each study participant will be negligible. If this is the case, the pairwise orderings can be removed from the model.

For comparison of the volume-dependent cardiovascular and metabolic effects between the groups G750 (n = 19) and G1000 (n = 19) consuming CP, ED, or the single components caffeine or taurine, the reduced model was checked for significance of the volume effect. Depending on the result, the volume variable may be removed from the final model. In the final model, the treatment effect was checked for significance, and for each drink the estimated mean effect as well as P values for “difference from baseline” and “difference from CP” were obtained. This aimed at answering the second part of the study, investigating the cardiovascular and metabolic effects of a commercial ED and its single components caffeine, taurine, combination of both, and glucuronolactone in comparison to the CP. Statistical calculations were conducted with the use of IBM SPSS Statistics version 21 and R version 3.5.0 with the lme4 and lmerTest packages. A P value < 0.05 was considered significant. Although we investigated the influence of the drinks on several outcome variables, we decided not to correct for multiple testing. The main reason was that this would make it harder to detect (undesired) carryover and period effects, or alternatively to have different significance levels within analysis of a single model.

The volume-dependent subjective tolerability of the products to identify unfavorable vegetative or neurological effects was assessed using a standardized query of symptoms by questionnaire in an ordinal scale (no, mild, moderate, severe). This was performed by the study staff (TP0-TP2) or by the participants themselves (after discharge, TP3, and TP4). The symptoms queried were palpitations, tremor, nausea, vomiting, restlessness, sweating, dizziness, fatigue, muscle spasms, euphoria, headache, and inebriation.
Energy drinks induce cardiovascular changes

Results

This randomized, double-blind crossover trial included 38 normal-weight adults (BMI 23.0 ± 1.7 kg/m²), 19 men and 19 women of young age (22.3 ± 1.8 y) without medical history of relevant cardiovascular, neurological, or other disorders. Table 1 shows the basic characteristics of the study population, stratified by intervention groups G750 (n = 19) and G1000 (n = 19). We observed no baseline differences between the groups G750 and G1000 (Table 1).

Cardiovascular and metabolic effects of G750 compared with G1000

Administration of an ED in the G1000 group showed a greater increase in serum caffeine concentration from baseline to TP1 (ΔTP1-TP0: 6.19 ± 1.44 mg/L compared to the G750 group (ΔTP1-TP0: 4.88 ± 1.15 mg/L; P < 0.01, data not shown). We observed a higher increase in serum caffeine concentration after administration of CP + C in the G1000 group (ΔTP0-TP1: 6.85 ± 2.15 mg/L) compared to the G750 group (ΔTP0-TP1: 5.25 ± 1.58; P < 0.05). We observed no significant effects of the volume on different cardiovascular and metabolic parameters (Supplemental Table 2). When the G750 and G1000 groups were analyzed together, all caffeine-containing study products led to an increased serum caffeine concentration compared to both baseline and the CP (P < 0.001, Figure 3A).

Symptoms

The severity of symptoms was mostly classified as mild. More than half of the participants developed ≥1 symptom (from mild to severe) during the study across all study products and volumes. Without consideration of mild symptoms, 11–37% of participants reported moderate to severe symptoms (Table 2). Interestingly, we observed a high percentage of participants reporting ≥2 symptoms after administration of ED, especially in the high volume (Table 2).

Five out of 38 individuals developed severe symptoms; interestingly, only after administration of ED or CP + C (data not shown). After ED administration at 1000 mL, 1 participant reported severe nausea, and another participant developed severe tremor. Two individuals experienced severe tremor after administration of CP + C at 750 mL. Moreover, CP + C at 750 mL led to severe restlessness in 1 participant. Cardiac arrhythmia was not detected in any of the participants.

Cardiovascular effects of ED and its components

The second part of the present study investigated the cardiovascular and metabolic effects of ED and its components in 6 study products. Because we did not observe any effect of the volume, we used all available data from all participants of the study together (from 38 participants for CP, ED, CP + C, and CP + T, and from 15 participants for CP + C + T and CP + G). Our results indicate that for the different products divergent effects were observed for MAP, systolic and diastolic BP, and QTc interval 1 h after consumption (ΔTP1-TP0).

Administration of the CP caused no differences between TP0 and TP1 regarding cardiovascular effects, (Figure 3B–F, Supplemental Table 3). Compared to baseline, administration of an ED caused an increase of MAP and systolic BP (P < 0.05 and P < 0.01, respectively, see Figure 3D + E and Supplemental Table 3) and a prolongation of the QTc interval (P < 0.01, see Figure 3B and Supplemental Table 3). Moreover, EDs accelerated the HR compared to baseline (P < 0.01, see Figure 3C and Supplemental Table 3). Also compared to the CP, EDs elevated BP (P < 0.01) and HR (P < 0.01) (Figure 3C–F).

Administration of both CP + C and CP + C + T increased MAP compared to baseline (P < 0.001 and P < 0.05, respectively). In the same time interval, CP + C also increased both systolic and diastolic BP (P < 0.001 and P < 0.01, respectively), whereas CP + C + T only increased diastolic BP (P < 0.05). All other study products had no effect on BP. The QTc interval was shortened after 1 h compared to baseline by the administration of CP + C + T and CP + G (both P < 0.05). Compared to the CP, CP + C and CP + C + T induced increased BP parameters, CP + C + T and CP + G caused a shortened QTc interval compared to CP (both P < 0.05) and CP + C + T reduced HR compared to CP (P < 0.05; Figure 3B–F and Supplemental Table 3).

Figure 4 shows changes in systolic and diastolic BP over 12 h. The increase in systolic BP was maximal after administration of CP + C (ΔTP1-TP0: 7.5 ± 7.8 mmHg after 1 h, P < 0.001), and returned to normal after 3 h. Also after administration of ED, systolic BP increased after 1 h (P < 0.05) and returned to normal after 3 h. After administration of CP + G, as well as after CP + C + T, systolic BP did not show significant differences after 1 h, but after the whole observation period of 11 h an elevation was observed compared to baseline (both P < 0.001), and also compared to CP (CP + C + T: P < 0.001, CP + G: P < 0.01). CP and CP + T had virtually no effect in this aspect (Figure 4A).

The time courses were similar, albeit less consistent, for diastolic BP after ED consumption. CP + C + T (P < 0.01) and CP + C alone (P < 0.05), but not CP + G, induced prolonged elevation of diastolic BP (Figure 4B).

Metabolic effects of an ED and its components

All study products caused a decrease in serum glucose and an increase in serum insulin concentrations 1 h after administration

TABLE 1 Characteristics of the study participants at baseline, randomized to 2 different volume interventions, and a subgroup with extended analyses

<table>
<thead>
<tr>
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<th>G750</th>
<th></th>
<th>G1000</th>
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<th>G1000</th>
<th></th>
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<tbody>
<tr>
<td>n</td>
<td>Male</td>
<td>Female</td>
<td>All</td>
<td>Male</td>
<td>Female</td>
<td>All</td>
</tr>
<tr>
<td>Age, y</td>
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<td>9</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.4 ± 12.0</td>
<td>64.4 ± 5.2</td>
<td>71.2 ± 11.3</td>
<td>77.6 ± 5.8</td>
<td>63.8 ± 5.8</td>
<td>70.3 ± 9.1</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.80 ± 0.09</td>
<td>1.68 ± 0.04</td>
<td>1.75 ± 0.1</td>
<td>1.81 ± 0.05</td>
<td>1.70 ± 0.05</td>
<td>1.75 ± 0.07</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 ± 1.9</td>
<td>22.7 ± 1.4</td>
<td>23.1 ± 1.7</td>
<td>23.8 ± 1.5</td>
<td>22.2 ± 1.7</td>
<td>22.9 ± 1.8</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>50.0</td>
<td>44.4</td>
<td>47.4</td>
<td>44.4</td>
<td>50.0</td>
<td>47.4</td>
</tr>
</tbody>
</table>

1Baseline characteristics of the study groups after randomization, given in mean ± SD or %; G750/G1000, study groups for test of 2 volumes, 750 or 1000 mL.
2In 19 participants per group a test of volume effects was conducted.
3Of the 19 participants in G1000 (test on volume effects), 15 agreed to take part in 2 further study days (second part of the study).
FIGURE 3  Cardiovascular and metabolic changes induced by 6 different study products. Changes of serum caffeine (A), QTc interval (B), heart rate (C), mean arterial pressure (D), systolic blood pressure (E), diastolic blood pressure (F), serum glucose (G), serum insulin (H), and modified HOMA-IR index (I) induced by administration of the 6 study products indicated in the x-axes. Data are presented as boxplots of changes from TP0 to TP1. P values indicate significant differences $\Delta TP1-TP0$ for each study product. Different from baseline, ** P < 0.01, * P < 0.05, (**) P < 0.1. Different from CP, ## P < 0.01, # P < 0.05, (##) P < 0.1. CP, control product; CP + C, control product with caffeine; CP + T, control product with taurine; CP + G, control product with glucuronolactone; CP + C + T, control product with caffeine and taurine; ED, energy drink; QTc interval, heart rate corrected duration of QT-segment in electrocardiography; TP, time point.
of the products compared to baseline values, corresponding to an elevation of the HOMA-IR. In particular, administration of an ED caused changes in parameters of glucose metabolism (Figure 3G-I and Supplemental Table 3). ED induced a relatively low reduction of glucose concentration ($P < 0.05$) and marked increase in insulin ($P < 0.001$) and HOMA-IR ($P < 0.001$). The metabolic changes caused by EDs were particularly different compared to the CP. The reduction of glucose serum concentration was less pronounced in EDs ($P < 0.001$). The effects of EDs on both insulin and HOMA-IR (both $P < 0.001$) were more substantial than those of CP. Regarding the changes in glucose concentration, CP + C ($P < 0.001$ compared to CP) had similar effects to the ED.

The electrolytes potassium (Supplemental Table 3), sodium, and calcium (data not shown) did not show any changes compared to baseline nor to other study products 1 h after consumption ($\Delta TP1-TP0$; after adjustment for multiple testing).

### Discussion

The present study evaluated the effects of a representative commercial ED and its major components on cardiovascular and metabolic parameters in young and healthy individuals. Apart from cardiovascular and metabolic effects, we studied tolerance and safety of 2 volumes (750 mL and 1000 mL) of the ED and other study drinks containing corresponding concentrations of the relevant agents. This amount is regularly reported by consumers, but might bear a health risk. We found that both volumes were reasonably tolerated subjectively. Therefore, a subsequent test series was performed only with the higher volume of 1000 mL. To our knowledge, the present study examines for the first time cardiovascular and metabolic effects of the major components of EDs (caffeine, taurine, glucuronolactone, or a combination of caffeine and taurine) to determine whether adverse effects of such EDs can be attributed to 1 component or to an additive reaction.

The present study revealed that consumption of an ED increases the MAP 1 h after administration. This is in accordance with findings from other studies, showing a significant average MAP increase of $3.8 \pm 0.7$ mmHg within 120 min ($P < 0.0005$) (30) and a MAP increase of $4.6$ mmHg (3.0–6.3 mmHg) between baseline and 30 min after administration (31). However, another study showed no significant change in MAP after administration of an ED (32). The present study indicates that caffeine (CP + C) also causes a significant increase in MAP 1 h after administration. Effects of the other study products were not notable, although also an increasing effect of CP + C + T on MAP was proven. We noted that CP + T alone appeared to reduce MAP; however, this was not statistically significant. Thus, we suspect that it is mainly caffeine that causes the observed increase in MAP after consumption of EDs, but our study provides evidence that this effect might be somehow attenuated by taurine. It appears that caffeine has the potential to stimulate and potentiate sympathomimetic actions, leading to elevations in BP (33). Taurine, on the other hand, exerts several potentially cardioprotective actions, for example, positive inotropy, decreased BP, or decreased platelet aggregation (14). Yet, the available evidence is insufficient to infer a possible shared mechanism of caffeine and taurine in response to BP and MAP (33). Thus, further research is needed to determine the possible role of a combination of caffeine and taurine on BP and MAP changes.

We observed a significant effect on QTc interval prolongation, and an increase of HR after consumption of an ED. Previous scientific evidence provides conflicting findings regarding HR. In agreement with our study, after consumption of an ED, Grassler et al. (30) noted a significant increase of HR ($3.7 \pm 0.7$ beats/min; $P < 0.05$), reaching a peak at around 90 min. Steinke et al. (34) reported a significant increase in HR of 5–7 beats/min within 4 h of administration of an ED. However, other studies have not identified any significant changes in HR (32, 35, 36, 37), or observed a reduction in HR 15 min after consumption of an ED (38). Interestingly, no change was seen in HR or QTc interval 1 h after administration of the single components caffeine (CP + C) or taurine (CP + T). After administration of caffeine and taurine as a mixture (CP + C + T), we observed a decrease in HR by trend; however, this was not significant ($P = 0.08$), and a reduction in the QTc interval. Glucuronolactone (CP + G) caused a reduction in QTc, an effect that has—to the best of our knowledge—not been previously described in the literature. Our data are in line with findings of a previous investigation showing a decreased HR within 45 min of ingesting capsules containing caffeine and taurine (39). Therefore, an additive effect of taurine and caffeine leading to a reduction of HR and QTc interval could be hypothesized. However, in our study, increased HR and a prolonged QTc interval were observed after ED consumption. So far, these effects caused by ED cannot be explained by any of the tested components caffeine, taurine, or glucuronolactone. We assume that other ED ingredients, for example, niacin or inositol could contribute to the cardiovascular effects, but this

### Table 2

Number of symptoms occurring 1 h after consumption of the 4 different study products administered to study participants in 2 different volumes (G750 and G1000)

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<th>G750</th>
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<tr>
<td></td>
<td>CP</td>
<td>ED</td>
<td>CP</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 19)</td>
<td>(n = 19)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Participants with any symptoms, n(%)</td>
<td>15 (79%)</td>
<td>15 (79%)</td>
<td>15 (79%)</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>Participants with moderate to severe symptoms, n(%)</td>
<td>4 (21%)</td>
<td>4 (21%)</td>
<td>6 (32%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Number of symptoms, n(%)</td>
<td>1</td>
<td>4 (21%)</td>
<td>3 (16%)</td>
<td>6 (32%)</td>
</tr>
</tbody>
</table>

1 Number of occurring symptoms reported by participants, given in total numbers (percentage). CP, control product; CP + C, control product with caffeine; CP + T, control product with taurine; ED, energy drink; G750/G1000, study groups for test volumes 750 or 1000 mL.
was not investigated in this study. For example, niacin has been shown to affect the cardiovascular parameters HR and heart rhythm (19, 25). Altogether, it should be considered that EDs contain multiple substances with possible interactions and synergisms exerting their effects in a dose-dependent manner (2, 5, 8–10).

In total, in our healthy participants, we noted previously suggested adverse effects of EDs on MAP, QTc interval, and HR. However, the adverse effects were marginal and possibly too small for short-term clinical consequences, at least in healthy individuals. We did not observe any objectively documented cardiac arrhythmia during the study. However, considering current evidence from case reports about cardiac rhythm abnormalities observed after ED consumption (9), it cannot be excluded that a combined effect of several changes in cardiovascular parameters may become clinically relevant to some individuals. It has been suggested that EDs are harmful to individuals at higher cardiovascular risk; the increased HR and prolongation of the QTc interval induced by EDs are considered risk indicators for heart rhythm disorders in vulnerable individuals (8). Such changes could be critical in individuals with acquired or congenital history of cardiovascular disease (8), diabetes, or in those taking medications, such as diuretics, cardiac glycosides, or psychotropic drugs (28, 40, 41). A cardiovascular risk from consumption of EDs could be assessed for patients with hypertension and hypertension-risk groups, such as patients in kidney failure, morbibly obese individuals, patients with valvular heart disease, pregnant women, and especially for those who already suffer from hypertension-related complications or congenital or acquired abnormalities of the vascular system (8, 18, 40, 42). Not all consumers are aware that they belong to such risk groups. Also CYP1A2 polymorphisms can influence cardiovascular response to EDs. Previous studies noted that carriers of a slow CYP1A2*1F allele have a higher risk for myocardial infarction and hypertension because of impaired caffeine metabolism (43, 44). Therefore, carriers should abstain from caffeinated drinks, including EDs. Along with possible cardiovascular symptoms, the main effects of EDs were identified as gastrointestinal upset or neurological side effects (agitation or tremor), sometimes requiring hospitalization (45). In the present study, 7 of 38 participants developed notable symptoms, that is, tremor and nausea, after consumption of an ED. The present study provides further evidence of unintended side effects, but is too small to draw final conclusions about safety and side effects.

Apart from the cardiovascular effects, we found that EDs decrease postexposure insulin sensitivity. Consumption of an ED caused a marked increase in insulin serum concentration, but at the same time only a moderate reduction of serum glucose, corresponding to a high HOMA-IR index. Although we observed HOMA-IR increases after administration of all other study products, in particular after CP + C, only ED caused a significantly higher HOMA-IR increase compared to the CP. Such effects have been reported in the literature only for caffeine, which impaired glucose tolerance by approximately 30% (46), but, so far, no study has examined the impact of EDs on glucose tolerance and insulin sensitivity.

Limitations of the present study include the limited number of volunteers that participated in this elaborate study, the selected study population, and the lack of large-range volume-responses and long-term observations. The BP measurement was carried out with use of automated BP monitors, so errors cannot be ruled out. The measurements of insulin metabolism were not performed by established procedures in a triplicate manner or at several consecutive TPs, and thus can be regarded as limited in reliability (29).

In conclusion, the present study determined that ED consumption causes significant adverse changes in BP, HR,
and glucose metabolism in young and healthy individuals. The clinical impact of these changes cannot be evaluated definitively within the present study. Although it is likely that caffeine causes increase in MAP, the other cardiovascular and metabolic effects of EDs cannot be attributed easily to the single components caffeine, taurine, or glucuronolactone. The clinical impact of the adverse changes could be of relevance to individuals at risk for cardiovascular or metabolic disease.

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