Abstract

Objective: Energy drink consumption is increasing among the population, especially adolescents and young adults. The health effects of energy drinks are unknown. In this study, we investigate the effects of low caffeine energy drinks on endothelial functions assessed by flow-mediated dilation (FMD) of the brachial artery.

Methods: Thirty healthy volunteers (15 men, 15 women) aged 19 to 46 years participated in the study. Flow-mediated dilation measurements of the brachial artery were performed and recorded per protocol. The volunteers were asked to drink 355 mL of energy drink containing 53.25 mg of caffeine after baseline measurements, and all measurements were repeated 60 minutes later. Baseline and post-energy drink values were compared.

Results: Systolic blood pressure (p=0.592), diastolic blood pressure (p=0.714), and heart rate values (p=0.056) were similar before and after the consumption of energy drinks. Preocclusion arterial diameters (p=0.236) and blood velocities (p=0.447) did not change after energy drink consumption. FMD levels were 9.2%±4.6% and 8.1%±4.7%, respectively, before and after energy drink consumption (p=0.176). Women had a 3% increase in preocclusion arterial diameters after energy drink consumption, whereas men had a 2.6% decrease (p=0.026)

Conclusion: Low caffeine energy drinks containing 53.25 mg of caffeine/355 mL can did not have any influence on blood pressure, heart rate, or endothelial functions in healthy volunteers.

Keywords: energy drinks, endothelial dysfunction, flow-mediated dilation, caffeine

Introduction

Energy drink consumption has been increasing among the younger populations in recent years (1, 2). Although a few countries have imposed age restrictions for the sale of energy drinks, high caffeine energy drinks generally are readily available to adolescents and young adults. According to a recent survey, two-thirds of children aged 13 to 17 years have consumed energy drinks at least once in their lives, and 41% of them have had them in the past three months (3). Among all the age groups, adolescents are the group with the highest energy drink consumption rates; and more than half of both adults and adolescents consume energy drinks mixed with alcohol (1). These drinks contain high amounts of caffeine and are marketed with claims to increase endurance and physical and mental performance. The main ingredients are artificial caffeine, sugar, taurine, and glucuronolactone. Inositol, vitamins (niacin, pantothenic acid, B6, B12), flavorings, and colorants (caramel, riboflavin) are also included.

With their increasing popularity, the reports of adverse events caused by energy drink consumption have also increased. Case reports and studies have shown that energy drink consumption might be related to hypertension, fatal arrhythmias, strokes, reverse takotsubo syndrome, myocardial infarctions, and sudden cardiac death (4-9). Studies conducted with energy drinks have also shown that they cause increase in blood pressure and heart rate depending on the amount of caffeine they contain (10). More than half of the reported adverse effects of energy drinks are...
related to the cardiovascular system (11). The exact mechanisms of how energy drinks adversely affect the cardiovascular system are not known. Acute hemodynamic changes in heart rate, blood pressure, and peripheral vascular resistance can lead to an increased cardiac workload, and endothelial dysfunction and proaggregatory potential could also be responsible for the adverse cardiovascular events (12, 13). Turkish Food Codex statement on energy drinks limits the amounts of several ingredients present in energy drinks. The legal limits are lower than 150 mg/L for caffeine, 200 mg/L for inositol, 2400 mg/L for glucuronolactone, and 4000 mg/L for taurin. The statement also bans energy drinks that contain more than 0.05% of alcohol. A 250 mL can of energy drink can contain a maximum of 37.5 mg caffeine, whereas a similar volume energy drink generally contains ≥80 mg caffeine in most other countries.

Endothelial dysfunction plays a central role in the pathophysiology of diseases such as atherosclerosis, hypertension, and diabetes. Endothelial dysfunction occurs before atherosclerotic morphological changes occur and may lead to plaque development and clinical complications (14). Atherosclerosis starts at a young age and progresses silently for a long time (15); the factors that cause endothelial dysfunction at young ages are likely to cause clinical atherosclerosis at later ages. Flow-mediated vasodilation or flow-mediated dilation (FMD) of the brachial artery is a non-invasive technique that measures the dilation of the brachial artery in response to reactive hyperemia after a five-minute occlusion of the vessel. Because of the method’s non-invasive nature and relative simplicity, it is the most commonly used method in determining endothelial functions.

There have been very few studies investigating the effects of high-caffeine energy drinks on endothelial functions. To the best of our knowledge, no studies have investigated the effects of low-caffeine energy drinks on endothelial functions thus far. In this study, we aimed to investigate the acute effect of a low-caffeine energy drink on endothelial functions as determined by brachial artery flow-mediated dilation.

**Methods**

Thirty healthy volunteers between the ages of 19 and 46 years were included in this single-center, open-label study. The study was approved by the Local Ethics Committee and conducted according to the principles of the Declaration of Helsinki. Healthy volunteers over 18 years of age and who gave consent for participation were included. Volunteers with any known chronic illness or acute infection, heavy caffeine consumers (>200 mg/day), those who smoked > five cigarettes/day, low body mass index (BMI) (<18.5) or obese individuals (BMI >30), pregnant or using oral contraceptives, those who had resting blood pressures <90/50 mm Hg, and those who did not give consent for participation were excluded. Volunteers were asked to fast for at least six hours before the examination and not consume caffeine containing beverages or cigarettes within the previous 12 hours. They were also advised not to exercise strenuously for 12 hours before the examination.

**Flow-mediated vasodilation measurements**

All examinations were performed between 8:00 am and 12:00 pm at room temperature between 22°C–24°C, in a semi-dark and calm environment. The subjects were asked to lie down in the supine position, and electrocardiographic monitoring was performed. After resting for 10 minutes, blood pressure and heart rates were measured on the left arm. The cuff of the sphygmomanometer was then placed in the middle of the right forearm. FMD examination was performed according to the guidelines proposed by Thijssen et al. (16) A 13.0 MHz linear array transducer (Vivid 7, Wipro GE Healthcare, GE Medical Systems Inc., Chicago, USA) was placed and scanned 5–6 cm above the antecubital fossa for scanning the longitudinal section of the brachial artery position where there were no folds and tortuosity, and the intimal layer was clearly displayed. The skin was marked with a pen as a guideline for further measurements. After the anatomical structures around the vessel were noted, basal measurements for vessel diameter and flow velocity were recorded. All measurements were made at the peak of the R wave on the ECG. For vessel diameter, measurements were made from the intima of the anterior vessel wall to the intima of the posterior wall. Three consecutive measurements on the same image were averaged. The pulsed wave (PW) Doppler sample volume was then placed parallel to the vessel, and flow velocity measurements were performed. After the basal measurements, the sphygmomanometer cuff was inflated to >50 mm Hg above the systolic blood pressure occluding the vessel for five minutes. The cuff was then deflated, and PW flow velocities were measured at the 15th second. Two-dimensional grayscale images for brachial artery diameters were monitored for three minutes in the post-deflation hyperemia phase. Diameters were measured in still images recorded in 15-second intervals; three consecutive measurements on the same image were averaged. The largest measurement was recorded as the peak diameter. Pre-occlusion and peak measurements in a volunteer can be seen in Figure 1.
After the basal measurements, the volunteer was asked to drink a 355 mL can of the energy drink (Red Bull®) containing 53.25 mg of caffeine, 284 mg of taurin, and 39 mg of sugar within 20 minutes. The volunteer was asked to wait in a sitting position for 60 minutes. After 60 minutes, blood pressure and heart rate measurements were repeated in the supine position, and the examination was repeated. FMD values were calculated using the formula given below.

\[ \text{FMD} \% = \frac{\text{peak arterial diameter at hyperemia} - \text{basal arterial diameter}}{\text{basal arterial diameter}} \times 100 \]

**Statistical analysis**

The sample size calculated to determine a 2.5% absolute change in FMD values with at least 80% power and 0.05 type 1 error was 29. The Statistical Package for the Social Sciences version 15 software (IBM Corporation Armonk, New York, USA) package was used to evaluate the data obtained in the study. The baseline parameters were compared with post energy drink consumption values by paired samples t-test or Wilcoxon signed ranks test depending on the normality of the distribution tested by the Shapiro-Wilk test. Data were expressed as median (minimum-maximum) and/or mean ± standard deviation for continuous data. Student’s t-test was used to determine the difference between male and female patients. P values <0.05 were considered significant.

**Results**

Thirty healthy volunteers (15 men, 15 women) between the ages of 19 and 45 years were included. The volunteers were healthy, non-obese individuals with a mean BMI of 24.2±5.3 kg/m².

**Effects on blood pressure and heart rate**

Basal systolic blood pressure was 111±11.4 mm Hg, diastolic blood pressure was 72.3±7.9 mm Hg, and heart rate 72.6±9.5 beats/min. There was no significant change in systolic or diastolic blood pressures or heart rates before and 60 minutes after consumption of the energy drink. The results did not change when systolic and diastolic blood pressure levels were corrected for age and BMI using the formula:

\[ \text{Corrected BP} = \frac{\text{BP} \times \text{age} \times \text{BMI}}{\text{mean age} \times \text{BMI of that sex}} \]

**Effects on flow-mediated dilation**

Pre-occlusion arterial diameters and flow velocities were similar before and after energy drink consumption (diameters 3.72±0.7 mm before energy drink, 3.76±0.6 mm after energy drink, \( p=0.236 \); flow velocities 28.9±24.9 cm/s before energy drink, 18.8±20.4 cm/s after energy drink, \( p=0.447 \)). Median time to peak diameter was 75 seconds. Post-deflation peak diameters and flow velocities were also similar before and after energy drink consumption (peak diameter 4.07±0.7 mm vs. 4.06±0.7 mm, \( p=0.787 \); flow velocity 43.3±30.4 cm/s vs. 42.3±31.4 cm/s, \( p=0.663 \)). Mean FMD was 1.58% lower after energy drink consumption, but that did not reach statistical significance. The results did not change when artery diameters were corrected for age and BMI using the formula:

\[ \text{Corrected diameter} = \frac{\text{diameter} \times \text{age} \times \text{BMI}}{\text{mean age} \times \text{BMI of that sex}} \]

**Differences in response to energy drink consumption according to sex**

Men had a mean 1.7% reduction, and women had an 8.1% increase in systolic blood pressures after energy drink con-
After ED, men had a 3% increase in pre-occlusion diameters after energy drink consumption, and the difference was statistically significant (p = 0.056). Similarly, men had a decrease of 2.6% in mean pre-occlusion diameters after energy drinks, whereas women had a 3% increase in pre-occlusion diameters after energy drink consumption, and the difference was statistically significant (p = 0.026). Changes in diastolic blood pressure, heart rate, and peak diameters were similar between men and women. Differences in response to energy drinks according to sex are summarized in Table 2.

### Discussion

This single-center open-label study demonstrated a neutral effect of low-caffeine energy drinks on endothelial functions as determined by FMD. The effects of energy drink consumption on hemodynamic parameters and heart rhythm have been extensively investigated. However, studies investigating the effects of energy drinks on endothelial functions, which play a crucial role in the development of cardiovascular diseases, are very few; and the results have been contradictory (17-21). Although most of these studies have shown detrimental effects of energy drinks on endothelial functions, some studies showed neutral results or even improvement in the endothelial functions. Most of these studies had small sample sizes and are difficult to compare because of the variability in the compositions of the different energy drinks used and the different methods used to assess endothelial functions. One study found that not all energy drinks have the same effects on endothelial functions, and caffeine might not be responsible for the differences (18). However, even the energy drink containing the lowest amount of caffeine was still higher than that used in our study.

Grasser et al. (21) measured microvascular endothelial function by iontophoresis and laser Doppler flowmetry. Similar to our study, they have found that endothelial functions did not change after ingestion of 355 mL of an energy drink containing 114 mg of caffeine. However, heart rate and blood pressure were increased, which might be a consequence of the higher caffeine content of the energy drink used.

Higgins et al. (19, 22) investigated the effects of a 710 mL can of an energy drink containing 240 mg of caffeine in young, healthy adults in two different studies and found a deterioration in the endothelial functions after 90 minutes in both. The caffeine content of the energy drink used in these studies was 4.5 times higher than the energy drink used in our study.

The lowest amount of caffeine in an energy drink tested in this study was 114 mg of caffeine. Higgins et al. (19, 22) have demonstrated the detrimental effect of an energy drink containing 80 mg of caffeine on endothelial function by peripheral arterial tonometry hyperemia index and an increase in platelet reactivity. Although the caffeine amounts studied in this study are the closest to our study, they have found that endothelial functions did not change after ingestion of 355 mL of an energy drink containing 114 mg of caffeine. However, heart rate and blood pressure were increased, which might be a consequence of the higher caffeine content of the energy drink used.

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The lowest amount of caffeine in an energy drink tested for its effect on endothelial functions was used in the study by Worthley et al. (20). They have demonstrated the detrimental effect of an energy drink containing 80 mg of caffeine on endothelial function by peripheral arterial tonometry hyperemia index and an increase in platelet reactivity. Although the caffeine amounts studied in this study are the closest to our study, the use of peripheral arterial tonometry in determining endothelial functions might be responsible for the conflicting results between the studies. It was shown that peripheral arterial tonometry, which primarily evaluates the microvascular bed, does not correlate with FMD (23-25). FMD is a valuable technique for investigating the responses of larger conduit arteries. The vasodilatory response of a medium-sized conduit artery such as the brachial artery is more nitric oxide (NO) dependent, but more complex non-NO dependent mechanisms are responsible for the hyperemic responses in the microvascular bed (25).
A noteworthy finding in this study was the difference in the responses to energy drink consumption in men and women. Women had an increase in systolic blood pressures and pre-occlusion artery diameters in response to energy drinks, whereas men had a decrease in these parameters. The modulatory effect of estrogens on the molecular pathways involved in endothelial function might explain this difference (26). The smaller vessel diameters in women may also have made the measurements more prone to errors.

The low-caffeine energy drink had no significant effects on heart rate or blood pressure. The studies with higher caffeine energy drinks yielded mixed results, with a majority observing an increase of one or more variables, such as the systolic blood pressure, diastolic blood pressure, or heart rate (10, 19, 22, 27-29). Differences in the volumes and caffeine contents of the energy drinks used in these studies, differences in methods used to determine the hemodynamic variables (such as central vs. peripheral blood pressure recordings), and different timing of measurements after energy drink consumption might explain these discrepancies. The amounts of caffeine in the energy drinks used in those studies varied between 80 and 240 mg, which is 1.5–4.5 times that of the energy drink used in our study.

Study limitations

This study had several limitations. First, the vessel diameter analysis was made manually on still images recorded at 15-second intervals. Although frequent image acquisition could have made it possible to determine the peak vessel diameter as accurately as possible, an automated vessel analysis on continuous recordings could have determined the peak vessel diameters more accurately. Second, the volunteers were only examined after consuming an energy drink; water might have been used as a control to understand the effect of ingestion of a similar volume of fluid on hemodynamic parameters. Finally, FMD and hemodynamic parameters were measured at only the 60th minute. Although this time point was determined by the studies showing that the effects of energy drinks start at 60 minutes (21), this single measurement might have missed the peak effect of energy drinks.

Conclusion

Consumption of a single 355 mL can of energy drink containing 53.25 mg of caffeine had a neutral effect on endothelial function. The majority of the adverse hemodynamic effects are attributed to caffeine or interaction between caffeine and sugar, whereas other ingredients are thought to play a minor role in cardiovascular effects (12). As caffeine is held responsible for most of the cardiovascular effects of energy drinks, low-caffeine energy drinks might be a safer alternative.

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