THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Cardiovascular and Cerebrovascular Response to RedBull® Energy Drink Intake in Young Adults

ABSTRACT

Background: Energy drinks contain caffeine, taurine, sucrose, vitamins, and other amino acids. The dosage of these varies depending on the drink chosen. Several studies on energy drinks have been carried out, but the results obtained are still inconsistent as well as the risk associated with consumption. This study analyzed the cardio- and cerebrovascular responses after consumption of an energy drink – RedBull® – under standardized pre- and post-ingestion conditions and its impact on the cardiovascular and cerebrovascular system.

Methods: A sample of 30 healthy young adult females was recruited and subjected to 3 moments of evaluation: at baseline, 30 minutes after ingesting the energy drink, and 60 minutes after ingesting it according to a non-randomized pre–post intervention study design.

Results: It is found that over time there are significant changes in peak systolic velocity ($P = .006$) and endodiastolic velocity ($P < .001$) of common carotid artery, peak systolic velocity ($P = .007$), and endodiastolic velocity ($P < .001$) of internal carotid artery, peak systolic velocity ($P = .004$), end endodiastolic velocity ($P = .013$) of the external carotid artery, endodiastolic velocity ($P = .042$) of the middle cerebral artery, cardiac output ($P = .004$), and heart rate ($P < .001$).

Conclusions: After the consumption of Redbull®, there was a decrease in the velocities of the carotid arteries and the middle cerebral artery as well as a decrease in cardiac output accompanied by a decrease in heart rate and a slight, although not significant, increase in systolic and diastolic blood pressures. However, it is still unclear which pathophysiological mechanisms are responsible for these changes.

Keywords: Energy drink, carotid arteries, middle cerebral artery, peak systolic velocity, endodiastolic velocity

ORIGINAL INVESTIGATION

INTRODUCTION

Energy drinks contain caffeine, taurine, sucrose, vitamins, and other amino acids[1], and their dosage varies depending on the beverage chosen. These drinks are classified by the Food and Drug Administration and other regulatory authorities as food supplements and not as food, so in many countries there is no limit imposed on the maximum content of caffeine used or of other ingredients.[2]

Caffeine is believed to be the active ingredient in energy drinks and is primarily responsible for the observed post-ingestion effects. At the physiological level, caffeine is characterized as an adenosine receptor antagonist, and thus a central nervous system stimulant, as well as a phosphodiesterase inhibitor. Caffeine is believed to increase exercise endurance and improve cognition and mood when the individual is fatigued or in sleep deprivation. In contrast, caffeine has both chronotropic and inotropic effects, so it can cause coronary and cerebral vasoconstriction, smooth muscle relaxation, electrolyte changes, and a decrease in insulin sensitivity, and it even has a ventilatory effect and promotes an increase in heart rate (HR), peripheral vascular resistance,[3] and blood pressure.[4]

Endothelial cells release vasodilator substances, such as nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, and vasoconstrictor substances, namely angiotensin II, thromboxane B2, and endothelin-1.[4] As mentioned

Rita Costa[1]
Clara Rocha[2,3,4]
Helder Santos[1]

[1]*Department of Clinical Physiology, Polytechnic Institute of Coimbra, Coimbra Health School, Coimbra, Portugal*
[2]*Department of Complementary Sciences, Polytechnic Institute of Coimbra, Coimbra Health School, Coimbra, Portugal*
[3]*Department of Electrical and Computer Engineering, INESC Coimbra, University of Coimbra, Coimbra, Portugal*
[4]*Laboratory for Applied Health Research (LabinSaúde), Coimbra, Portugal*

Corresponding author:
Clara Rocha
✉ clarapr@estescoimbra.pt

Received: July 24, 2022
Accepted: October 21, 2022
Available Online Date: January 1, 2023

Cite this article as: Costa R, Rocha C, Santos H. Cardiovascular and cerebrovascular response to RedBull energy drink intake in young adults. *Anatol J Cardiol.* 2023;27(1):19-25.

DOI:10.14744/AnatolJCardiol.2022.2315

above, caffeine is an adenosine receptor antagonist.[5] Adenosine has a vasodilatory effect, which is mediated by inducing NO release from endothelial cells via the adenosine A2 receptor. Since caffeine acts as an antagonist of adenosine 2A receptors, it leads to a decrease in NO production, resulting in endothelial dysfunction, thus breaking down hemostasis and causing vasoconstriction and increased peripheral vascular resistance. In contrast, caffeine has also the ability to increase NO through A1 adenosine receptors and inhibitors, increasing endothelial function. The dosage of caffeine seems to be the predominant factor in choosing which pathway is used. The increase in NO may also be induced by the increase in calcium, resulting from its release from the sarcoplasmic reticulum by its relationship with adenosine receptors. Caffeine is also a phosphodiesterase inhibitor, causes the accumulation of cyclic adenosine monophosphate, and leads to an increase in free calcium and consequently a decrease in intracellular calcium. Low calcium levels lead to an inhibition of protein kinase phosphorylation and, as a result of this inhibition, changes occur in the actin–myosin interaction, and this is one of the pathways for the development of arrhythmias.[4] Endothelial dysfunction may also increase the risk of thrombosis, inflammation, and reduction of coronary flow by the loss of ability to regulate vascular resistances.[6]

The other component of energy drinks that has been previously mentioned is taurine, an amino acid abundant in the central nervous system that acts in neuronal growth and protection, cellular metabolism, osmoregulation, and glycolysis, and whose effects refer to a reduction in blood pressure and, to a increase in stroke volume by suppressing sympathetic nervous stimulation , and influencing calcium stores in cardiac muscle.[3,4]

Regarding sucrose, which results from the combination of glucose and fructose, the dose in energy drinks is believed to be able to affect the cardiovascular system, providing an increase in HR, increasing cardiac output and having a controversial action on peripheral vascular resistances: glucose decreases peripheral vascular resistances while fructose tends to increase them. A physiological justification for the occurrence of such changes is that after ingestion, there is an increase in blood glucose inducing a rapid increase in plasma insulin; the increase in insulin concentration causes cardiac stimulation, consequently increasing cardiac output. The differential impact of vascular resistance through increased sympathetic activation may be an important mechanism to explain the observed disparity in blood pressure response.[3,4]

HIGHLIGHTS

- Energy drinks are classified as food supplements, so there is no limit imposed on the maximum content of caffeine used or of other ingredients.
- A sample of 30 healthy young adult females was recruited and subjected to 3 moments of evaluation: at baseline, 30 minutes after ingesting the energy drink, and 60 minutes after.
- After the consumption of 250 mL of Redbull®, there was a decrease in carotid and middle cerebral artery velocities as well as a decrease in cardiac output associated with a decrease in heart rate and a slight increase.

Nowadays, we are confronted with a substantial increase in the consumption of these drinks, especially by young adults,[1,3-7] who are influenced by the alleged beneficial effects presented by the energy drink brands, whose information conveyed by them refers to increased performance, cognition,[4] as well as reaction speed, level of vigilance, metabolism, and general well-being.[1]

Despite the beneficial effects cited by these identities, several adverse effects have been described following consumption of these drinks, such as tachycardia, insomnia, and headache.[8,9]

Regarding the hemodynamic parameters, a literature review indicates that the results of different studies were not always coherent. In some investigations, the consumption of energy drinks does not cause changes in frequency, systolic,[10,11] and diastolic[12] blood pressures. In addition , the prolonged consumption of taurine, may be followed by a reduction in the risk of developing coronary artery disease, or even an alteration in the anticonvulsant and epileptogenic properties.[4] By contrast, some investigations found a statistically significant effect on HR and blood pressure.[1,13]

Therefore, as the results obtained are not always consistent and the risk associated with consumption is still uncertain,[3,4] it becomes very important to carry out more studies.

The purpose of this study was to investigate the cardiovascular and cerebrovascular responses after the consumption of an energy drink – RedBull® – under standardized conditions of pre- and post-ingestion and its impact on the cardiovascular and cerebrovascular system.

METHODS

The study was designed as a prospective study and was performed in accordance with the ethical standards and principles referred to in the Declaration of Helsinki. All participants were informed and clarified about the study procedures and signed an informed consent describing the objectives and work methods. The research project was accepted by the Ethics Committee of the Polytechnic Institute of Coimbra (no. 101 CEPC2/2020). Confidentiality and anonymity of the data collected were ensured, as they were collected for scientific purposes, without any cost or compensation to the participants.

Subjects

A population of 30 healthy young female adults aged between 18 and 22 years old was defined. Exclusion criteria were defined based on methodological information found in other articles[1,2,10,12,13] and defined as: body mass index (BMI) above 29.9 kg/m^2, individuals with cardiovascular diseases, namely arterial hypertension, and/or metabolic diseases such as diabetes mellitus and regular consumption of energy drinks; high competition athletes were also excluded from the study as well as pregnant women.

All participants were informed and clarified about the study procedures and signed an informed consent describing the objectives and work methods. Confidentiality and anonymity of the data collected were ensured, as they were collected for scientific purposes, without any cost or compensation to the participants.

Study Protocol

Participants were asked not to consume any caffeine derivative in the 24 hours before the study was conducted as well as not to smoke during that same period. (1) Each participant was submitted to 3 evaluation times: at baseline (T0), 30 minutes after ingestion of the energy drink (T1), and 60 minutes post-ingestion according to a non-randomized pre–post intervention study design (T2). The sample was obtained in a controlled environment, at a stable temperature between 22ºC and 24ºC. The entire collection process was performed by the same operator, and the measurement sites were standardized.

A questionnaire was conducted to collect the following data: age, anthropometric data, presence or absence of cardiovascular and/or metabolic disease (hypertension and/or diabetes mellitus), whether they use dietary supplements, whether they consume energy drinks and how regularly, if they take oral contraceptives, if they practice sports regularly, excluding high competition sports, if they are smokers, and if they are pregnant.

Data collection was performed with the participant in the supine position. A 5-minute rest period was given before the data collection; subsequently, the systolic diastolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured at the level of the right brachial artery, and the HR was also obtained. This measurement was performed 3 times with a Riester and Ri-ChampionN® model device (automatic oscillometric measurement).

At the ultrasound level, we standardized the data collection in the left side of each participant and used a GE Vivid T8® ultrasound scanner with a 6-12 MHz linear probe for the carotid study and a 3S MHz probe for the transcranial study; all the recording was performed with conventional electrocardiographic monitoring.

The participants consumed 250 mL of RedBull® at room temperature; a 250 mL can is composed of the following ingredients: water, sucrose, glucose, acidifier (citric acid), carbon dioxide, taurine (100 mg), acidity regulators (sodium carbonates, magnesium carbonates), caffeine (80 mg), flavors, colorings (plain caramel, riboflavins), and vitamins—20 mg niacin (vitamin B3), 5 mg pantothenic acid (vitamin B5), 2 mg vitamin B6, and 2 µg vitamin B12. As energy value, it has 195 kJ/46 Kcal per 100 mL (487 kJ/116 kcal per 250 mL).

Data Analysis

Values of the time elapsed between two secessive R-waves of the QRS signal on the electrocardiogram (RR-Interval-variance), SBP, DBP, systolic diameter (SD), diastolic diameter (DD), peak systolic velocity (PSV), and endodiastolic velocity (EDV) were measured as described above. HR was calculated from the appropriate RR interval. The mean arterial pressure (MAP) was calculated from DBP and SBP as follows: MAP = 1/3 (SBP + 2DBP) mm Hg. Pulse pressure (PP) was calculated as (SBP − DBP) mm Hg. Arterial distensibility coefficient was calculated as $2\pi\,(SD - DD)/(DD \times PP)$.[15,16] Compliance was calculated as $\pi \times DD \times (SD - DD)/2PP$ $mm^2\,mm\,Hg^{-1}$, by derivation of Reneman's formula.[14-16] Cerebrovascular resistance index (CVRI) was calculated as (PSV − EDV)/PSV.[1] Stiffness index ß was derived from log (SBP/DBP)/(SD − DD) × DD.[16] Estimated cardiac output (CO_{EST}) was computed by the formula of Liljestrand and Zander[19] as the product of PP/(SBP + DBP) and HR. All CO_{EST} values were then multiplied by a constant (*k*) to obtain $CO_{EST\text{-}ADJ}$ values.[17] Body mass index was calculated as the ratio of weight to height squared kg m^{-2}.

Statistical Analysis

Categorical variables were described by frequency and percentage and continuous variables by mean and SD. Shapiro–Wilk test was used to confirm the distribution of continuous variables. Levene test was used to verify the homogeneity of variances. ANOVA test for repeated samples was used to evaluate the behavior of continuous variables with normal distribution in the 3 collection phases. The Greenhouse–Geisser correction was applied whenever sphericity was violated, and the Bonferroni test was used for multiple comparisons. For the variables whose distribution did not follow a normal distribution, the Friedman test was used. *P*-values lower than .05 were considered as significant. Statistical analysis was performed by using software IBM SPSS® v.27 (National Opinion Research Center, Chicago, Ill, USA) and GraphPad Prism v. 6.04 (La Jolla, San Diego, Calif, USA).

RESULTS

We studied 30 young females with a mean age of 19.96 ± 1.13 years and a BMI of 21.27 ± 2.60 kg m^{-2}. About 26.67% practiced physical exercise with some, 6.67% had smoking habits, and 60% were taking oral contraceptives, and only 1 participant took food supplements (iron).

Systolic blood pressure showed mean values ± SD of 118.03 ± 1.39 mm Hg, 119.33 ± 1.81 mm Hg, and 118.60 ± 1.79 mm Hg at baseline, 30 minutes post-intake, and 60 minutes post-intake, respectively, as well as DBP values of 74.20 ± 1.24 mm Hg, 74.47 ± 1.19 mm Hg, 76.03 ± 1.39 mm Hg at baseline, 30 minutes post-intake, and 60 minutes post-intake, respectively. The HR shows values of 81.47 ± 2.48 bpm, 75.87 ± 2.24 bpm and 74.33 ± 2.19 bpm at baseline, 30 minutes post-ingestion, and 60 minutes post-ingestion, respectively.

Table 1 shows the mean values and SD of each variable analyzed in the sample, as well as their significance values during the evaluation. It was found that over time there are significant changes in PSV ($P = .006$) and EDV ($P < .001$) of the common carotid artery (CCA), PSV ($P = .007$) and EDV ($P < .001$) of the internal carotid artery (ICA), PSV ($P = .004$) and EDV ($P = .013$) of the external carotid artery (ECA), EDV ($P = .042$) in the middle cerebral artery (MCA), $CO_{EST\text{-}ADJ}$ ($P = .004$), and HR ($P < .001$). Post-hoc tests revealed statistically significant decreases from T0 to T1 in the HR ($\Delta = -6.9\%$; $P = .021$), PSV ($\Delta = -8.9\%$; $P = .004$) and EDV ($\Delta = -16.4\%$; $P = .001$) in the CCA, EDV ($\Delta = -13.96\%$; $P = .007$)

Table 1. Evolution of the Parameters Analyzed in the Group Through the Evaluation of the Energy Drink Ingestion

PARAMETERS	T0	T1	T2	*P*
Common carotid artery				
Systolic diameter, mm	57.20 ± 3.79	56.93 ± 3.91	56.90 ± 4.23	.870
Diastolic diameter, mm	50.93 ± 2.91	50.97 ± 3.08	50.87 ± 4.29	.980
Peak systolic velocity, $cm.s^{-1}$	99.67 ± 2.63	90.75 ± 2.14**	92.96 ± 2.85	.006
Endodiastolic velocity, $cm.s^{-1}$	22.68 ± 0.78	18.96 ± 0.65**	18.45 ± 0.60½½½	<.001
β	1.89 ± 0.17	2.19 ± 0.29	2.04 ± 0.27	.107
Internal carotid artery				
Peak systolic velocity, $cm.s^{-1}$	85.99 ± 2.66	79.48 ± 3.02	76.21 ± 2.72½	.007
Endodiastolic velocity, $cm.s^{-1}$	28.09 ± 1.13	24.17 ± 0.84**	22.35 ± 0.97½½½	<.001
External carotid artery				
Peak systolic velocity, $cm.s^{-1}$	74.76 ± 2.65	67.03 ± 2.51*	66.96 ± 2.46½½½	.004
Endodiastolic velocity, $cm.s^{-1}$	11.28 ± 4.60	9.20 ± 3.39*	10.72 ± 3.72£	.013
Middle cerebral artery				
Peak systolic velocity, $cm.s^{-1}$	97.53 ± 3.24	93.27 ± 3.08	92.11 ± 3.59	.256
Endodiastolic velocity, $cm.s^{-1}$	42.96 ± 1.63	39.44 ± 1.71*	39.24 ± 1.80½	.042
Pulse pressure, mm Hg	43.83 ± 0.90	44.87 ± 0.99	42.57 ± 1.14	.086
Mean arterial pressure, mm Hg	88.81 ± 1.22	89.42 ± 1.35	90.22 ± 1.43	.325
Cardiac output	18.46 ± 0.46	17.58 ± 0.61	16.28 ± 0.61½½	.004
Compliance $mm^2.mm\ Hg^{-1}$	11.49 ± 4.04	10.69 ± 4.19	11.33 ± 4.60	.407
Distensibility	0.018 ± 0.06	0.016 ± 0.01	0.018 ± 0.01	.496
Cerebrovascular resistance index	0.56 ± 0.09	0.58 ± 0.01	0.58 ± 0.01	.088
Systolic blood pressure, mm Hg	118.03 ± 1.39	119.33 ± 1.81	118.60 ± 1.78	.644
Diastolic blood pressure , mm Hg	74.20 ± 1.23	74.47 ± 1.19	76.03 ± 1.39	.162
Heart rate, bpm	81.47 ± 2.48	75.87 ± 2.24*	74.33 ± 2.19½½½	<.001

T0, baseline assessment. T1, assessment 30 minutes after ingestion of energy drink. T2, assessment 60 minutes after ingestion of energy drink. T0-T1: *$P < .05$, **$P < .01$; T0-T2: ½$P < .05$, ½½$P < .01$, ½½½$P < .001$; T1-T2: £$P < .05$.

in the ICA, PSV (Δ = −10.3%; $P = .016$) and EDV (Δ = −18.4%; $P = .026$) in the ECA, MCA EDV (Δ = −8.2%; $P = .047$), and from T1 to T2 in ECA EDV (Δ = 16.5%; $P = .031$). The variables HR (Δ = −8.8%; $P < .001$), EDV of the CCA (Δ = −18.7%; $P < .001$), ICA (Δ = −20.4%; $P < .001$) and MCA (Δ = −8.7%; $P = .032$), PSV of the ICA (Δ = −11.4%; $P = .011$), ECA (Δ = −10.4%; $P < .001$), and $CO_{EST-ADJ}$ (Δ = −11.8%; $P = .002$) show statistically significant decreases from T0 to T2.

DISCUSSION

Despite the vast literature that exists about the consumption of energy drink, and its potential effects on the cardiovascular system, there is no consensus on the results achieved, as well as the impact that energy drinks have on the cardiovascular and cerebrovascular level. Although there are studies where the cerebral blood flow was observed, there were none using the analysis and study of carotid arteries and their velocities by echo-Doppler.

In the study that was performed, there was a significant decrease in the HR parameter ($P < .001$); however, no statistically significant changes were found in SBP ($P = .644$), DBP ($P = .162$), PP ($P = .086$), and MAP ($P = .325$). These results are partially in agreement with the study by Nowak et al[10] in which no significant changes in SBP were recorded. In this study, contrary to the values we obtained, there was a significant increase in DBP and no significant changes in HR. Nevertheless, the results regarding these parameters are contradictory: in a study by Grasser et al.[1] there was a decrease in HR and an increase in SBP and DBP; however, in a study by Miles-Chan et al.[12] there was a significant increase in HR, as well as in MAP, SBP, and DBP. It still seems uncertain how energy drink affects blood pressure parameters and HR. At the pathophysiological level, the decrease in HR can be explained by some mechanisms,[2] namely Marey's reflex, or baroreflex,[20] where the decrease in HR is due to a compensatory response to increased blood pressure, or by direct stimulation of the vagus nerve through the caffeine present in energy drink.[2,21] In our study, we recorded a slight increase in SBP from the first to the second assessment (118.03 ± 1.39 vs. 119.33 ± 1.81), but this value is not statistically significant, so we cannot conclude precisely whether the baroreflex is a plausible justification for the results obtained. Nevertheless, the vagus nerve, X cranial pair, when stimulated is responsible for regulating HR, blood pressure and vascular resistances[22,23] could appear to be a better predictor of HR response to energy drink ingestion; however, caffeine acts as an antagonist of AI and A2 adenosine receptors and consequently would cause an increase in HR and blood pressure.[4,23] Another possibility is the action of taurine rather than caffeine, since taurine can cause the suppression of the sympathetic nervous system and influence the calcium channels in the cardiac muscle[3] or the simultaneous action of these 2 ingredients as well as sucrose. In our study, the HR decreases significantly, 6.9% in acute phase and 8.8% in late phase, leaving it unclear what mechanism is responsible for this decrease. It is also important to mention that in the study by Nowak et al.[10] 750 mL of energy drink was consumed and, in our study, only 250 mL was consumed; so the discrepancy in the amount of drink ingested may justify the different values obtained. Similarly, in the study by Grasser et al[1] only 355 mL of energy drink was consumed, and the HR results obtained support the data we obtained.

Liljestrand and Zander[19] proposed a formula to calculate the stroke volume by evaluating the blood pressure, and

consequently, from it, we could obtain the cardiac output by multiplying the value obtained in the expression by the HR. Different studies have shown that the proposed formula can provide the correct cardiac output data.[17,18] This expression does not allow obtaining absolute values and quantitatively characterize the cardiac output since the values obtained are not comparable with values obtained by the methods used today; however, it allows understanding the variation of cardiac output throughout the evaluation, and furthermore, in 1 of the studies, when a constant was added, *k*, that allowed converting the values, it showed that the results obtained by the original expression and by the expression with the constant were identical.[17] In our study, the results point to a decrease in cardiac output over time, showing statistically significant decrease of 11.8% from T0 to T2, which contradicts the results presented by Grasser et al.[1] Miles-Chan et al.[12] and Yamakoshi et al.[24] who obtained an increase in cardiac output. A possible explanation for the results obtained is due not only to the different amount of drink ingested, but also to the changes in HR, which influence, in a directly proportional way, cardiac output. Cardiac output can be calculated by multiplying the stroke volume by the HR; since there was a decrease in HR, there was consequently a decrease in the cardiac output. However, this decrease may be due to the decrease in velocities since these are directly proportional to the flow and inversely proportional to the surface area of the tube. It seems uncertain which pathway acts first on the other.

After an analysis of the variables obtained by carotid and transcranial ultrasound study, we can conclude that, in an acute phase, there was a significant decrease in the peak systolic velocity and EDV of the CCA (8.9% and 16.4%, respectively) and ECA (10.3% and 18.4%, respectively) and in the EDVs of the ICA (13.96%) and MCA (8.2%). Although not significant, the PSV of the ICA decreases by 7.6% between evaluations, as does the MCA, which decreases by 4.4%.

At the late phase level, we can state that there was a statistically significant decrease in CCA (18.7%), ICA (20.4%), and MCA (8.7%) EDVs, as well as ICA (11.4%) and ECA (10.4%) peak systolic velocities. Although not significant, there was a decline of 6.7% in PSV of the CCA, as well in ECA with a decline of 5.0% and 5.6% in the MCA.

Through the study of the mechanics of fluids, the flow velocity can be calculated by the expression $V = Q/(\pi R^2)$, so the velocity varies directly proportionally with the flow and inversely with the radius of the tube. In the acute phase, which does not show significance values and in the late phase, where it shows a statistically significant alteration, the cardiac output decreases, which may justify the decrease in velocities, since the decrease in cardiac output, by the expression mentioned above, decreases the velocities. However, the opposite may be true, and it remains uncertain. By Ohm's law, we know that the flow can be obtained by dividing the difference between pressures by the resistance, where the difference between pressures varies directly with the flow and resistances vary inversely proportionally. On the other hand, according to Poiseuille's law, flow can also be obtained by the following expression $Q = [(SBP - DBP) \times R^4]/8VC$, with *R* being the tube radius, *V* the blood viscosity, and *C* the tube length. Thus, a decrease in flow rate may be due essentially to a decrease in pressure differences or a decrease in radius. When assessing the SD and DD of the CCA, we did not obtain statistically significant changes; the values of the CCA SD went from 57.20 ± 3.79 mm to 56.93 ± 3.91 mm and the CCA DD from 50.93 ± 2.91 mm to 50.97 ± 3.08 mm. However, it is known that small changes in the diameter of a vessel can lead to large changes in flow conduction capacity. On the other hand, the difference between pressures, PP, is influenced by the injection volume of the heart and vascular distensibility, and in the acute phase it increases slightly from 43.83 ± 0.90 mm Hg to 44.86 ± 0.99 mm Hg, and in the late phase it decreases from 43.83 ± 0.90 mm Hg to 42.57 ± 1.14 mm Hg, so the decrease in output may be due to the decrease in radius as well as the increase in the resistances.

Chuang et al[25] concluded that flow velocities have a prognostic value in cardiovascular disease, namely low values of EDV are associated with an increased risk of cardiovascular disease; however, carotid artery diameters do not appear to be predictors of it.

Caffeine, present in energy drinks, is, as mentioned above, an adenosine receptor antagonist. Adenosine has a vasodilatory effect since it induces the release of NO from endothelial cells. Caffeine can influence the vasculature in 2 different ways; however, in our study, due to the significant decrease in endodastolic velocities in all arteries observed, we believe that caffeine acted as an antagonist of the adenosine A1, at inhibitory receptors, causing a release of NO, thus leading to vasodilation and consequent decrease in velocities studied, causing changes in hemostasis.[5]

This endothelial dysfunction caused by caffeine consumption may be even more significant when it comes in contact with other ingredients, namely taurine and sucrose, since taurine has the ability to suppress the sympathetic nervous system and influences calcium channels,[4] while sucrose has a disparate behavior on vascular resistances, since glucose decreases peripheral vascular resistances and fructose increases.[3,4] Mills et al[26] concluded with their study that caffeine consumption influences the biodisponibility of NO, a vasodilator, causing an increase in endothelium-dependen t dilation. In contrast, Molnar et al[27] states that it is not caffeine that promotes increased endothelial function since, in their study, for 2 drinks with the same amount of caffeine, the energy drink potentiated vascular changes while caffeine alone did not significantly influence endothelial function. Miles-Chan et al[12] raised the hypothesis that the energy drink directly affects the myocardium and caffeine alone affects the vasculature, obtaining divergent responses in relation to systemic vascular resistances, in which the energy drink has diminished them. In our study, the most significant changes we obtained were in the EDVs, leading us to believe that there is a significant relaxation of the artery, causing, consequently, vasodilation. With the decrease in blood flow velocities and the decrease in flow itself, we can hypothesize that these results are a compensatory response to the

increase in peripheral vascular resistances. The interaction between the ingredients of energy drinks seems to be the main explanation for these changes, and future studies will be necessary to find out which of these ingredients has a more predominant role in the effects that energy drinks have at the cardiovascular level.

The cerebrovascular analysis of the MCA velocities shows a noticeable decrease in the velocities throughout the evaluation, with a significant decrease in the EDV, 8.2% in acute phase and 8.7% in late phase, and a slight increase in the CVRI, 3.6% in both phases; this increase may be due to a more significant decrease in the EDV compared to the PSV (4.4% in acute phase and 5.6% in late phase). One of the mechanisms that may be responsible for this vasodilation, in addition to the increased bioavailability of NO, is an increase in the concentration of CO_2 at the brain, since it acts as a vasodilator at the cerebrovascular level.[28,29] In the study by Grasser et al.[1] cerebral blood flow velocity also decreased after energy drink consumption and an increase in CVRI was also observed; however, after energy drink consumption, end tidal CO_2 decreased so it is suggestive that the decrease in velocity and increase in CVRI are due to the variations in CO_2 levels. The decreases in MCA velocities seem to question the beneficial effects presented by energy drink marketers, such as reaction speed and level of vigilance,[1] so even during our study, some participants reported the same symptom, i.e., sleepiness.

Study Limitations

This study has some limitations. One of the most important limitations of the present study is the lack of an adequate control group with a placebo drink. Another limitation was the sample size and follow-up times of the study which were not sufficiently long for the analysis of the systemic and cardiological effects of the Redbull drink. Therefore, it would be important to increase the number of subjects as well as the long-term follow-up period to improve the power of future studies. Finally, the same-sex sample is also a limitation of our study.

CONCLUSIONS

In conclusion, our results showed that after consumption of Redbull®, an energy drink, there was a decrease in carotid and middle cerebral artery velocities, as well as a decrease in cardiac output associated with a decrease in HR and a slight increase, even if not significantly, in systolic and DBP. However, it is important to carry out further studies to clarify which pathophysiological mechanisms are responsible for these changes. It would also be interesting to study each ingredient in energy drinks in the future, in order to find out which one has the greatest impact on the cardiovascular and cerebrovascular system.

Ethics Committee Approval: All participants were informed and clarified about the study procedures and signed an informed consent describing the objectives and work methods. The research project was accepted by the Ethics Committee of the Polytechnic Institute of Coimbra (no. 101 CEPC2/2020 in 2020) and was performed in accordance with the ethical standards and principles referred to in the Declaration of Helsinki. Confidentiality and anonymity of the data collected were ensured, as they were collected for scientific purposes, without any cost or compensation to the participants.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.C, H.S.; Design – R.C, C.R., H.S.; Supervision – C.R., H.S.; Data Collection and/or Processing – R.C, H.S.; Analysis and/or Interpretation – R.C, C.R., Literature Review – R.C.; Writing – R.C.; Critical Review – C.R., H.S.

Acknowledgments: The authors would like to thank the participants who agreed to participate in the study project and the Coimbra Health School for the availability and provision of equipment, especially Professors Jorge Conde and Telmo Pereira, for the relevant contribution to this project.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This work has been partially supported by project grant UIDB/00308/2020.

REFERENCES

1. Grasser EK, Yepuri G, Dulloo AG, Montani JP. Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr*. 2014;53(7):1561-1571. [CrossRef]
2. Hajsadeghi S, Mohammadpour F, Manteghi MJ, et al. Effects of energy drinks on blood pressure, heart rate, and electrocardiographic parameters: an experimental study on healthy young adults. *Anatol J Cardiol*. 2016;16(2):94-99. [CrossRef]
3. Grasser EK, Miles-Chan JL, Charrière N, Loonam CR, Dulloo AG, Montani JP. Energy drinks and their impact on the cardiovascular system: potential mechanisms. *Adv Nutr*. 2016;7(5):950-960. [CrossRef]
4. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics*. 2011;127(3):511-528. [CrossRef]
5. Higashi Y. Coffee and endothelial function: A coffee paradox? *Nutrients*. 2019;11(9):2104. [CrossRef]
6. Higgins JP, Yang B, Herrin NE, et al. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. *World J Cardiol*. 2017;9(2):162-166. [CrossRef]
7. Butler AE, Qian W, Leatherdale ST. Caffeinated energy drink consumption and predictors of use among secondary school students over time in the COMPASS cohort study. *Prev Med Rep*. 2019;15:100911. [CrossRef]
8. Hammond D, Reid JL, Zukowski S. Adverse effects of caffeinated energy drinks among youth and young adults in Canada: a Web-based survey. *CMAJ Open*. 2018;6(1):E19-E25. [CrossRef]
9. Malinauskas BM, Aeby VG, Overton RF, Carpenter-Aeby T, Barber-Heidal K. A survey of energy drink consumption patterns among college students. *Nutr J*. 2007;6:35. [CrossRef]
10. Nowak D, Gośliński M, Nowatkowska K. The effect of acute consumption of energy drinks on blood pressure, heart rate and blood glucose in the group of young adults. *Int J Environ Res Public Health*. 2018;15(3):544. [CrossRef]
11. Chtourou H, Trabelsi K, Ammar A, Shephard RJ, Bragazzi NL. Acute effects of an "energy drink" on short-term maximal performance, reaction times, psychological and physiological

parameters: insights from a randomized double- blind, placebo-controlled, counterbalanced crossover trial. *Nutrients*. 2019; 11(5):992. [CrossRef]
12. Miles-Chan JL, Charrière N, Grasser EK, Montani JP, Dulloo AG. The blood pressure-elevating effect of Red Bull energy drink is mimicked by caffeine but through different hemodynamic pathways. *Physiol Rep*. 2015;3(2):e12290. [CrossRef]
13. Steinke L, Lanfear DE, Dhanapal V, Kalus JS. Effect of "energy drink" consumption on hemodynamic and electrocardiographic parameters in healthy young adults. *Ann Pharmacother*. 2009;43(4):596-602. [CrossRef]
14. Kool MJ, van Merode T, Reneman RS, Hoeks AP, Struyker Boudier HA, Van Bortel LM. Evaluation of reproducibility of a vessel wall movement detector system for assessment of large artery properties. *Cardiovasc Res*. 1994;28(5):610-614. [CrossRef]
15. Hoeks AP, Brands PJ, Reneman RS. Assessment of the arterial distension waveform using Doppler signal processing. *J Hypertens Suppl*. 1992;10(6):S19-S22. [CrossRef]
16. Miyachi M, Kawano H, Sugawara J, et al. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation*. 2004;110(18):2858-2863. [CrossRef]
17. Koenig J, Hill LK, Williams DP, Thayer JF. Estimating cardiac output from blood pressure and heart rate: the liljestrand & zander formula. *Biomed Sci Instrum*. 2015;51:85-90.
18. Zhang J, Critchley LA, Huang L. Five algorithms that calculate cardiac output from the arterial waveform: a comparison with Doppler ultrasound. *Br J Anaesth*. 2015;115(3):392-402. [CrossRef]
19. Liljestrand G, Zander E. Vergleichende Bestimmungen des minutenvolumens des Herzens beim Menschen mittels der stickoxydulmethode und durch Blutdruckmessung. *Z gesamte exp med*. 1928;59(1):105-122. [CrossRef]
20. Mosqueda-Garcia R, Tseng CJ, Biaggioni I, Robertson RM, Robertson D. Effects of caffeine on baroreflex activity in humans. *Clin Pharmacol Ther*. 1990;48(5):568-574. [CrossRef]
21. Whitsett TL, Manion CV, Christensen HD. Cardiovascular effects of coffee and caffeine. *Am J Cardiol*. 1984;53(7):918-922. [CrossRef]
22. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: Part I. *Headache*. 2016;56(1):71-78. [CrossRef]
23. Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Res Brain Res Rev*. 1992;17(2):139-170. [CrossRef]
24. Yamakoshi T, Matsumura K, Hanaki S, Rolfe P. Cardiovascular hemodynamic effects of Red Bull® Energy Drink during prolonged, simulated, monotonous driving. *Springerplus*. 2013;2(1):215. [CrossRef]
25. Chuang SY, Bai CH, Cheng HM, et al. Common carotid artery end-diastolic velocity is independently associated with future cardiovascular events. *Eur J Prev Cardiol*. 2016;23(2):116-124. [CrossRef]
26. Mills CE, Flury A, Marmet C, et al. Mediation of coffee-induced improvements in human vascular function by chlorogenic acids and its metabolites: two randomized, controlled, crossover intervention trials. *Clin Nutr*. 2017;36(6):1520-1529. [CrossRef]
27. Molnar J, Somberg JC. Evaluation of the effects of different energy drinks and coffee on endothelial function. *Am J Cardiol*. 2015;116(9):1457-1460. [CrossRef]
28. Grüne F, Kazmaier S, Stolker RJ, Visser GH, Weyland A. Carbon dioxide induced changes in cerebral blood flow and flow velocity: role of cerebrovascular resistance and effective cerebral perfusion pressure. *J Cereb Blood Flow Metab*. 2015;35(9):1470-1477. [CrossRef]
29. Brian JE Jr. Carbon dioxide and the cerebral circulation. *Anesthesiology*. 1998;88(5):1365-1386. [CrossRef]