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Review

Cardiovascular Complications of Energy Drinks

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Abstract: Energy drinks (EDs) are gaining popularity every year with a broad consumer base including athletes, amateur competitors, and even those experiencing work-related fatigue. Evidence indicates that a significant number of individuals who consume EDs experience resultant morbidity and/or mortality, with a preponderance of cases involving teenagers and young adults. Adverse effects of ED consumption may occur in healthy persons, however certain individuals may be particularly susceptible to complications. At-risk populations include those of young age, the caffeine-naïve, or caffeine-sensitive, pregnant women, competitive athletes, and those with underlying cardiovascular disease. This paper summarizes the cardiovascular complications associated with ED use and provides suggestions on consumption of these drinks in various populations.

Keywords: energy drink; cardiovascular complications; caffeine; myocardial infarction; arrhythmia; QTc interval

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1. Introduction

Energy Drinks (EDs) represent a relatively new class of caffeinated beverages that are marketed to improve energy, athletic performance, concentration, endurance, and weight loss [1–4]. It is important for both healthcare providers and consumers to recognize the difference between these new products and traditional soft drinks such as coffee, tea, sports drinks (such as Gatorade™), sodas, juices, or flavored water [5]. One group describes them this way: "Energy drinks are the Wild West of the soft drinks industry: often shockingly and unnecessarily high in sugar and caffeine..." [6].

EDs contain various substances including taurine (an amino acid), niacin, pyridoxine, cyanocobalamin (B12), riboflavin (B2), ginseng extract, glucuronolactone (a glucose metabolite), inositol (B8), guarana (contains caffeine, teobromin, and teofiline), ephedra, yohimbine, Ginkgo biloba, kola nut, theophylline, sugars, vitamins, herbs, and L-carnitine [7].

Examples of foods and beverages caffeine content are freely available [8,9]. It is important to note that while caffeine concentration varies amongst beverages, all EDs or energy shots surpass the FDA official soft drink concentration limit, as demonstrated by Figure 1.

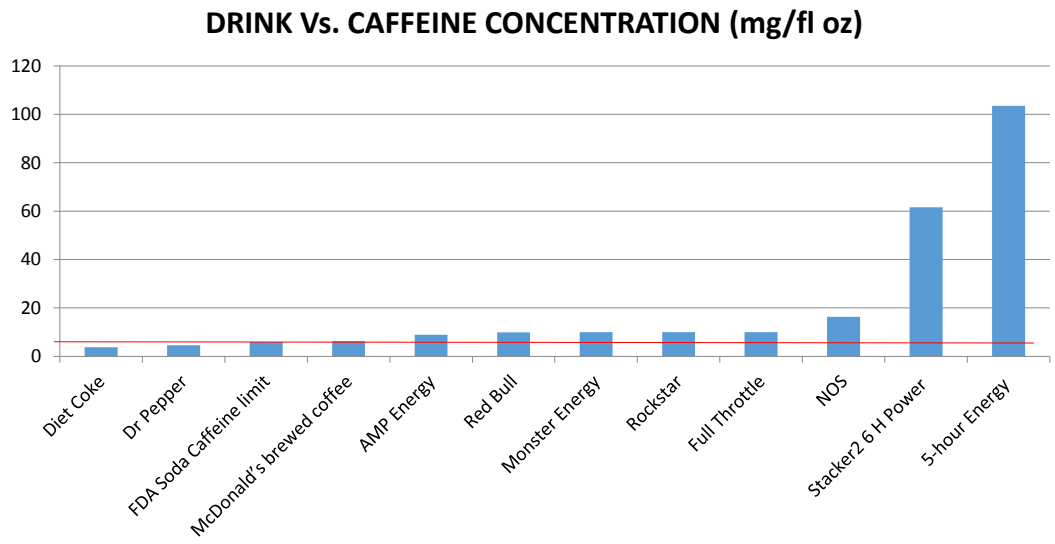

Figure 1. Various drinks and their caffeine concentration. Note red horizontal line specifies the FDA imposed limit of 71 mg caffeine/12 fl oz soda.

The FDA imposes a limit of 71 mg of caffeine per 12 fl oz of soda (200 parts per million) or 0.2 mg of caffeine per mL [2]. A typical ED contains 0.34 mg of caffeine per mL, 2–4 times the amount seen in one serving of regular soda or tea and slightly more than regular filtered coffee [8,9]. Some EDs do not disclose caffeine content at all or may fail to account for the caffeine contributed by "energy blend" ingredients (guarana, kola nut, yerba mate) [10,11].

The pharmacology of these substances, reports of toxicity, and an increase in emergency room visits associated with ED consumption all raise concern for the potentially severe adverse events linked with ED use [12].

Safe limits of caffeine consumption are still undetermined but data suggest that most healthy adults can safely consume up to 400 mg per day [8]. Pregnant women should avoid excessive caffeine use as high intake is associated with known risk factors for adverse reproductive outcomes although up to

200 mg per day is likely safe [13,14]. The FDA consumer report states that no safe levels of caffeine consumption have been determined in children [2].

Targeted advertising of EDs towards younger consumers is concerning as they represent a particularly vulnerable population [15]. Adolescents are more likely to experience side effects due to higher rates of caffeine-naivety and the tendency to consume larger quantities of these beverages [16]. Despite the risk, consumption of EDs is highest among adolescents/young students and declines with increasing age [13]. EDs are now consumed by 30%–50% of adolescents, with 31% of 12–19 year-olds reporting regular use [2,15]. Young adults are also consuming EDs: in Minneapolis/St. Paul, a survey of 2287 participants (55% female, mean age 25.3 years) found 19% consumed EDs at least weekly [17]. Another recent study of 1620 nursing students noted 1265 students (78.1%) reported ED use, averaging 1.6 ± 2.6 cans per week, ranging from 1 to 30 cans per week [18].

ED consumption has been associated with lower breakfast frequency, higher sugar-sweetened soda intake, video game use, unhealthy dietary and weight-control behaviors, insomnia, later alcohol and substance use ($p < 0.05$) [17,19,20].

Alcoholic beverages prepared with EDs are popular amongst adolescents and college students [21]. This practice has been associated with an increase in unhealthy habits including heavy alcohol consumption, cigarette smoking, and illicit drug abuse [22–24]. Harmful consequences include driving while impaired, riding with an intoxicated driver, and sexual abuse have been reported more frequently by adolescents and young adults who combined EDs with alcohol [25,26]. Moreover, alcohol consumption can increase the half-life of caffeine by up to 72%, which may potentiate the ED exposure effects [27].

Emergency department visits related to complications of ED consumption are increasing in frequency [28,29]. In 2011, of 2.3 million calls to the US National Poison Data System, 4854 were ED-related [30]. About half the cases of ED-related toxicity involved unintentional exposures by children <6 years old [30]. It is important to note that not all cases reported developed toxicity, but rather involved exposures to potentially toxic substances. Consumption of EDs have been associated with multiple medical complications including seizures, anxiety, agitation, hallucinations, migraines, pontine myelinolysis, gastrointestinal upset, rhabdomyolysis, metabolic acidosis, insomnia, arrhythmias, chest pain, and other cardiovascular complications [2,30–34].

This review will focus on those involving the cardiovascular system. It is important to remember that much of the data presented are derived from case reports reporting associations, so it is difficult to make strong conclusions. However, in some areas such as hemodynamic effects and endothelial dysfunction, studies with reasonable numbers of subjects are presented upon which stronger conclusions can be derived.

2. Cardiovascular Complications

Cardiovascular complications of consuming EDs may be related to acute or chronic exposure. These are listed in Table 1 and are detailed below.

Table 1. Cardiovascular complications associated with energy drink (ED) consumption.

Acute Effects	Potential Chronic Effects
Elevated Blood Pressure	Hypertensive Heart Disease
Increased Heart Rate	Coronary Artery Disease
Increased Corrected QT (QTc) Interval	Atherosclerosis
Supraventricular Arrythmia	Cerebrovascular Disease
Ventricular Arrythmia	Peripheral Arterial Disease
Coronary Artery Spasm	
Coronary Artery Thrombosis	
Takotsubo Cardiomyopathy	
ST-Segment Elevation Myocardial Infarction (STEMI)	
Aortic Dissection	
Postural Orthostatic Tachycardia Syndrome	
Sudden Cardiac Death	
Endothelial Dysfunction	

2.1. Acute Effects

2.1.1. Elevated Blood Pressure

Numerous studies have associated EDs and their ingredients with acute hypertension [35,36]. This is consistent with known hemodynamic changes caused by caffeine consumption [1,8]. Acute caffeine consumption can increase plasma renin, catecholamines, and dopamine. These substances stimulate the central nervous system, thereby increasing blood pressure and heart rate [11,37]. In addition, synergistic effects between components of the "energy blend" used in EDs may also have an effect on blood pressure [35]. The effects of caffeine on hemodynamics can last up to 5 h after ingestion. Such effects may be amplified by performing physical activity just after consumption [38–40].

One study of 25 young, non-obese, and healthy subjects (12 women, mean age 22.5 years, mean body mass index (BMI) 23.3 kg/m^2) who had cardiovascular measurements performed before and 2 h after the ingestion of either 355 mL of the ED or 355 mL of tap water showed an overall negative hemodynamic profile in response to ingestion of Red Bull® (Red Bull GmbH, Fuschl am See, Austria) ED. Notable findings included elevated blood pressure, increased double product (systolic blood pressure × heart rate), and lower cerebral blood flow velocity [35]. Specifically, when compared to baseline values, Red Bull® ED ingestion led to increases both in SBP and DBP of 5.2 and 6.1 mmHg, respectively.

Another study of 15 healthy 18–40 year olds had them consume two cans of ED (500 mL) daily for 1 week. Each can contained 200 mg caffeine and 1000 mg taurine [41]. Within 2–4 h of ED consumption, on Days 1 and 7, systolic blood pressure increased by 7.9% ($p = 0.006$) and 9.6% ($p < 0.001$) and

diastolic blood pressure increased by 7.0% (p = 0.046) and 7.8% (p = 0.063). Importantly, the subjects did not habituate to this effect after a week.

Another study randomized nine subjects (5 females, mean age 27.7 years) to receive either an ED (80 mg caffeine and 1000 mg taurine in 8.3-oz Red Bull®) or control (80 mg caffeine solution in 8 oz water) every 3 to 4 h on a single day and followed 24-h ambulatory BP monitoring [42]. Mean 24-h systolic blood pressure, diastolic blood pressure, and mean arterial pressure recordings were significantly higher in the ED group than in the control (123.2 *vs*. 117.4 mm Hg, 73.6 *vs*. 68.2 mm Hg, 90.1 *vs*. 84.8 mm Hg, respectively).

Blood pressure is a direct function of cardiac output and therefore also dependent on cardiac stroke volume. To test whether EDs increase stroke volume, one group did a double-blind crossover study: 13 conditioned athletes performed exhaustive endurance exercise at three different times [40]. Prior to exercise, they ingested either Red Bull® ED, a similar caffeine drink without taurine, or placebo. Echocardiography was done before ingestion, before exercise, 40 min after ingestion, and in the recovery period. Stroke volume was significantly increased in only the Red Bull® ED group recovery period (80 mL before ingestion *vs.* 98 mL). This was mainly due to the reduced end-systolic volume. Thus, consumption of Red Bull® ED increased cardiac contractility, suggesting that caffeine and taurine together were causal.

Another study evaluated cardiac magnetic resonance images of 32 healthy volunteers (mean age 28 years) at baseline and 1 h post-consumption of a caffeine and taurine containing ED. ED consumption led to a significant increase in peak systolic strain rate 1 h after consumption [43]. This was not observed in the caffeine only group. Again, this suggests that the combination of caffeine and taurine was the causal effect.

A study of 50 young, healthy subjects (mean age 25 year old, BMI 25.6 kg/m^2, 60% males) measured heart rate and blood pressure 2 h after consumption of 355 mL of Red Bull® ED: their systolic blood pressure increased from 112 to 121 mmHg (p = 0.006), and diastolic blood pressure 73 to 76 mmHg (p = 0.008) [36].

For healthy individuals, occasional minor fluctuations in blood pressure are unlikely to cause significant side effects and blood pressure often returns to normal after cessation of ED consumption [44]. However, for those who are already undergoing treatment for hypertension, elevations in blood pressure may be significant and as such, it is recommended that these individuals avoid EDs [1]. Furthermore, case reports of otherwise healthy children developing hypertension from habitual use of EDs have been noted [44].

Summary: A typical increase in systolic and diastolic blood pressure in normal healthy persons 1–2 h following consumption of ED is approximately 6–10 mmHg and 3–6 mmHg respectively.

2.1.2. Increased Heart Rate

Acute consumption of EDs has been associated with small but significant increases in heart rate.

One study of 25 young non-obese and healthy subjects (mentioned above) showed a steady increase in heart rate in the Red Bull® ED group relative to water load, with values reaching a peak around 90 min (3.7 ± 0.7 beats per minute) [35].

Another study enrolled 15 healthy 18–40 year olds (mentioned above) noted that within 2–4 h of ED consumption, on Days 1 and 7, heart rate increased by 7.8% ($p = 0.009$) and 11.0% ($p < 0.001$) [41].

A study of 50 young, healthy subjects (mean age 25 year old, mentioned above) noted heart rate on average increased from 78 to 85 beats per minute ($p = 0.005$) [36].

Summary: The heart rate in normal healthy persons 1–2 h following consumption of ED increases by approximately 3–7 beats per minute.

2.1.3. Increased Corrected QT (QTc) Interval

A significantly increased QTc interval in healthy young subjects, as well as those with a preexisting genetic long QT syndrome, has been reported in association with consumption of EDs. EDs contain many ingredients in addition to caffeine including taurine, often present in high amounts, which is known to work on multiple cardiac ion channels and in certain circumstances can be arrhythmogenic [45].

One study of 15 healthy 18–40 year olds (mentioned above) noted that on Days 1 and 7, QTc interval increased by 2.4% ($p = 0.368$) and 5.0% ($p = 0.052$) [41].

One case involved a 22 year old female who had consumed six cans of a caffeinated ED within 4 h. She then suffered an out-of-hospital cardiac arrest at a discotheque, with initial rhythm revealing torsade de pointes polymorphic ventricular tachycardia [46]. Importantly, hospital tests for drugs or alcohol were negative. Her QTc obtained by emergency medical services on site of the occurrence was initially noted to be 526 ms, 492 ms in the intensive care unit, and eventually returned to a normal value of 419 ms. Genetic testing revealed type 1 long QT syndrome 1 (type 1 LQTS), KCNQ1 mutation. In this young female who had a preexisting long QT syndrome, the QT interval was prolonged following excessive ED consumption, likely precipitating her cardiac arrest.

A 13-year-old girl was referred to clinic with type 1 LQTS after a prolonged QTc was discovered on an electrocardiogram completed two months prior, noted after the patient had consumed at least one 16-oz can of an ED (160 mg of caffeine) [47]. During the morning of her initial presentation, she had reported palpitations, chest pain, shakiness, and dizziness. She went to the emergency room when her pain worsened throughout the day. An electrocardiogram was performed on presentation and revealed a QTc of 561 ms with a heart rate of 108 beats per minute. A confirmatory follow-up electrocardiogram done 1 h later revealed a QTc of 557 ms at 96 bpm. She was admitted for overnight observation and continuous QTc monitoring. By the following day, QTc had normalized and she was subsequently discharged.

The QT prolongations observed in the preceding cases ranged from 25 to 107 ms. This is particularly concerning as the Food and Drug Administration suggests further testing when a change of greater than 10 ms is observed [48].

Summary: A typical increase in QTc in normal healthy persons 1–2 h following consumption of ED is up to 22–25 ms.

2.1.4. Supraventricular Arrhythmia

Consumption of caffeine has been associated with precipitation and/or exacerbation of supraventricular arrhythmia [49]. Other ingredients in EDs including “energy blends” and herbs could potentially trigger arrhythmias as well [15]. Atrial fibrillation has been observed following acute ingestion of EDs in young

adults [50]. It is unknown whether these individuals had a genetic predisposition towards arrhythmia or if ingredients in the EDs triggered the events [50]. It is important to note that atrial fibrillation is extremely rare in the pediatric population and it almost always occurs in association with structural heart disease [51].

A 13-year-old healthy boy in Spain developed atrial fibrillation with rapid ventricular response at 160 beats per minute during a soccer training session after consuming EDs [52].

A 23-year-old woman with no medical history was brought to the hospital for palpitations and chest tightness shortly after consuming a GNC Speed Shot (GNC Corporation, Pittsburgh, PA, USA) and a Mountain Dew (PepsiCo, Inc., Purchase, NY, USA) soda drink [53]. An electrocardiogram showed a narrow complex tachycardia with a ventricular rate of 219 beats per minute. After administration of 6 mg of adenosine by rapid intravenous push, she converted to normal sinus rhythm.

A 24-year-old man presented with palpitations, chest pain, and acute respiratory failure shortly after ingestion of an ED [54]. He was noted to have frequent runs of supraventricular and ventricular tachycardia. He was later diagnosed with Takotsubo cardiomyopathy (see below).

A 58-year-old previously healthy male was admitted with a history of worsening dyspnea and palpitations [55]. The patient admitted that he had recently been working extended hours and consumed one bottle (1000 mL) per week of a highly caffeinated (caffeine content 4.04 mg/mL) commercially available ED for six months. He was noted to be in atrial fibrillation with rapid ventricular response at 169 beats per minute. Echocardiography revealed a globally dilated heart with a globally reduced ejection fraction of 45%. Coronary angiography showed normal coronary arteries. After treatment with digoxin, ramipril, and warfarin, his heart rate returned to normal. Six months after discontinuing the ED, he was clinically improved and a repeat echocardiogram confirmed normal left ventricular dimensions and ejection fraction (65%).

Summary: Supraventricular arrhythmias, especially atrial fibrillation, can be seen in normal healthy persons following consumption of EDs.

2.1.5. Ventricular Arrhythmia

Ventricular arrhythmias, particularly ventricular tachycardia and ventricular fibrillation, may lead to cardiac arrest/sudden cardiac death and have been associated with ED consumption [10]. Caffeine is known to increase levels of circulating catecholamines, cause hypokalemia in a dose-dependent manner, and suppress sodium channel conduction, all of which may predispose patients to ventricular arrhythmias [10]. In addition, high doses of caffeine, like those found in EDs, may exacerbate cardiac conditions in which stimulants are contraindicated [2]. The most concerning of these are ion channelopathies and hypertrophic cardiomyopathy, the most prevalent genetic cardiomyopathy in children and young adults. These patients have an increased risk of hypertension, syncope, arrhythmias, and sudden death [2]. In addition to caffeine, taurine and guarana have proarrhythmic properties, making their consumption by patients with underlying structural heart disease potentially fatal [56].

A 28-year-old-man consumed three cans of ED 5 h before a basketball match and subsequently reported palpitations and nausea [57]. Thirty minutes into the game, during a break, the patient lost consciousness secondary to ventricular tachycardia. Normal sinus rhythm was achieved with cardioversion however the patient died on the third day of hospitalization.

A 25-year-old woman with pre-existing mitral valve prolapse developed intractable ventricular fibrillation leading to her death after consuming a "natural energy" guarana health drink containing a high concentration of caffeine [58]. On the day of her death she had consumed nearly all of a 55 mL squirt bottle of "Race 2005 Energy Blast with Guarana and Ginseng". She was noted to have a blood caffeine concentration of 19 mg/L. The caffeine concentration in the bottle of Race 2005 Energy Blast was assayed and yielded a caffeine level of 10 g/L, which is more than 60 times the concentration of caffeine in cola beverages.

After a day of motocross racing, a 28 year-old healthy man developed cardiac arrest after consuming 7–8 cans of an ED within 7 h [59]. The patient's initial cardiac rhythm was ventricular fibrillation; he was restored to sinus rhythm after receiving two 150 J biphasic direct-current shocks. An initial electrocardiogram showed sinus rhythm and elevated anteroseptal ST segments with reciprocal inferior ST depression. Urgent cardiac catheterization revealed diffuse coronary artery vasospasm believed to have been precipitated by the high levels of caffeine and taurine in his blood.

A 24 year-old male with no previous medical history collapsed while drinking a Red Bull® ED containing 80 mg caffeine and 1000 mg of taurine combined with vodka [60]. CPR was initiated. Emergency Medical Services arrived and found the patient to be in ventricular fibrillation. He was intubated, given amiodarone, naloxone, and epinephrine, and underwent defibrillation six times with eventual conversion to sinus rhythm with prolonged QRS duration. An electrocardiogram showed the presence of R′ (R prime) with ST segment elevation in V1 and V2 consistent with Brugada syndrome. An automatic implantable cardioverter defibrillator (AICD) was placed and he was discharged in a stable condition. The authors believe that Brugada syndrome was unmasked and provoked by the ED.

A 19 year-old man who consumed a Monster ED (160 mgs caffeine) and marijuana suffered a cardiac arrest [10]. He was found to be in ventricular fibrillation and was converted back into normal sinus rhythm. Extensive cardiac evaluation including laboratory, echocardiography, cardiac magnetic resonance imaging, coronary angiography, and electrophysiologic testing (including provocative testing) were normal.

A 57 year-old male suffered a cardiac arrest following consumption of multiple NOS (Coca-Cola Company, Atlanta, GA, USA) EDs (caffeine 1300 mg) [10]. He was noted to have left ventricular hypertrophy with regional wall motion abnormalities on echocardiography.

A 24 year-old presented with palpitations, chest pain, and acute respiratory failure shortly after ingestion of an ED [54]. He was noted to have frequent runs of supraventricular and ventricular tachycardia. He was later diagnosed with Takotsubo cardiomyopathy (see below).

A 45 year-old man with a history of tetralogy of Fallot repair at age 5 and AICD placement at age 40 experienced a potentially fatal arrhythmia consuming three Red Bull® ED over a period of 3–4 h [56]. The first AICD shock occurred within 30 min of completing the third ED and was preceded by feelings of lightheadedness and severe dizziness. Interrogation of the AICD revealed both ventricular tachycardia and ventricular fibrillation.

A 24 year-old Caucasian man with a history of mild hypertension presented to the emergency department with a one-hour history of crushing chest pain, nausea, and vomiting [61]. He had consumed about 20 cans of the ED "XL" in combination with 3,4-methylenedioxymethamphetamine. Electrocardiogram on admission showed widespread ST segment elevation confirming acute myocardial infarction. He was given aspirin, oxygen, and morphine. While awaiting coronary angiography, the patient developed ventricular fibrillation and subsequently died.

Summary: Ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) can be seen in normal healthy persons or in those with underlying Brugada Syndrome, usually following consumption of multiple EDs over a short period of time.

2.1.6. Coronary Artery Spasm

High caffeine content in EDs may be associated with competitive inhibition of adenosine receptors, resulting in catecholamine release. This causes rapid efflux of calcium from the sarcoplasmic reticulum of the vascular smooth muscle cells and can lead to coronary artery vasospasm. [62,63]. Also, taurine modulates calcium signaling and toxic levels can affect calcium concentration both intra- and extracellularly [11]. In addition, there is some evidence that taurine may enhance the physiologic actions of caffeine, leading to increased inotropy, and thus may contribute to coronary artery spasm [43,62].

A 19 year-old-man had been drinking 2–3 cans of Red Bull® ED daily for a week and presented with malaise for several hours. He then developed chest pain radiating to his right arm associated with feeling cold, clammy, and short of breath [62]. He was noted to have electrocardiogram changes consistent with an ST-segment elevation myocardial infarction; he received nitroglycerine and other standard medications. Coronary angiography revealed entirely normal coronary arteries with very mild left ventricular systolic impairment. His 12-h troponin I was significantly elevated at 34.67 μg/mL (normal range <0.07) confirming myocardial infarction. The authors believe that the diagnosis was likely coronary artery vasospasm induced by the exposure to the ED.

A 28 year-old man consumed 7–8 cans of an ED over 7 h. He later had sudden cardiac arrest after spending the day motocross racing [59]. He was found to have coronary artery vasospasm believed to have been precipitated by the high levels of caffeine and taurine in his blood (the only abnormalities found on his workup and testing).

A 17 year-old male presented with angina and an abnormal electrocardiogram concerning for ST-segment elevation myocardial infarction [64]. He reported drinking a disproportionate number of caffeinated EDs (3–4 Red Bull® 80 mg of caffeine/can and 2–3 Monster 160 mg of caffeine/can) the night prior to presentation. His peak Troponin T was 7.07 ng/mL. He improved following intravenous nitroglycerine and a presumed diagnosis of coronary artery spasm was made.

These coronary artery vasospasm cases described above are associated with high levels of caffeine (400–800 mg) as well as taurine (2000–8000 mg).

Summary: Coronary artery spasm may occur in normal healthy persons following consumption of multiple (2–8 cans) of EDs each containing 80–160 mg caffeine as well as 1000–2000 mg taurine.

2.1.7. Coronary Artery Thrombosis

A 24 year-old healthy African-American male presented to the emergency department with a 10-h history of nausea, emesis, palpitations, and severe retrosternal chest pressure. He reported that these symptoms began 2 h after consuming three drinks of vodka mixed with an ED [65]. It is important to note the potentially confounding effects of alcohol with such co-ingestions. He denied cocaine or other drug use. An initial electrocardiogram suggested acute myocardial infarction and he was urgently referred for coronary angiography. He was noted to have several large thrombi in his coronary arteries. Cardiac enzymes indicated a myocardial infarction with a Troponin I of 38 ng/mL. Following

intra-aortic balloon pump placement, emergent coronary artery bypass grafting was performed. A full hypercoagulable workup came back negative and he was discharged home on Coumadin.

Coronary artery thrombosis has been associated in a single case of a normal healthy person—following consumption of multiple (≥3 cans) EDs combined with alcohol (vodka).

2.1.8. Spontaneous Coronary Artery Dissection

A previously healthy 13 year-old boy was admitted to clinic after presenting with 2 h of acute-onset, "crushing", mid-sternal chest pain [66]. He had ingested an ED for the first time 10 h prior. The electrocardiogram revealed sinus rhythm with 2- to 3-mm ST-segment elevations in leads II, III, aVF, and V3 through V5. Echocardiography showed an estimated left ventricular ejection fraction of 54% and moderate apical hypokinesis. He was given aspirin, subcutaneous enoxaparin, sublingual nitroglycerin, enalapril, and metoprolol at presentation with relief of pain. However, the initial mildly elevated troponin I level of 0.65 ng/mL (normal range 0–0.06 ng/mL) increased to 3.96 ng/mL at 24 h. He therefore underwent coronary angiography which revealed extensive dissection of the left anterior descending coronary artery with a visible tear from the distal part of the vessel. Coronary blood flow was preserved so conservative medical management was chosen over intervention.

Summary: Spontaneous coronary artery dissection has been associated with ED consumption in one normal healthy child.

2.1.9. ST-Segment Elevation Myocardial Infarction (STEMI)

Amongst the aforementioned cases of STEMI caused by coronary artery spasm or stenosis, one was notable for accelerated atherosclerosis.

A 26 year-old Hispanic male presented with an acute STEMI. He had no known coronary risk factors and only reported a two pack-year smoking history and excessive ED consumption [66]. The patient reported consuming between eight and ten 473 mL cans of ED per day (Monster, Rockstar, and others). Cardiac catheterization subsequently confirmed total occlusion of his left circumflex coronary artery; the patient received a drug-eluting stent with resolution of his electrocardiogram changes. It is important to note that he was a smoker which could be a confounder as smoking is known to be associated with coronary artery disease.

Summary: ST-Segment Elevation Myocardial Infarction has been associated with excessive consumption of EDs (8 or more cans) in healthy persons.

2.1.10. Takotsubo Cardiomyopathy

EDs contain sympathomimetic substances such as caffeine. Caffeine is a competitive antagonist of adenosine receptors A1 and A2A in the central nervous system and myocardium, altering neurotransmitter release and increasing heart rate respectively [8]. Caffeine also induces catecholamine release and causes a rise in intracellular calcium within myocytes [8,43]. Of special relevance, EDs are often consumed in a rapid manner and to excessive amounts, which may predispose to a surge in catecholamines [67].

A 24 year-old man presented with palpitations, chest pain, and acute respiratory failure shortly after ingesting an ED [54]. Frequent runs of supraventricular and ventricular tachycardia were noted.

An echocardiogram revealed a moderately reduced left ventricular ejection fraction of 35% and basal hypokinesis. Admission electrocardiogram showed sinus tachycardia and nonspecific T-wave inversion in leads I and aVL. Cardiac magnetic resonance imaging with gadolinium administration on hospital day 10 showed moderate to severe hypokinesis of the basal segments of the left ventricle with apical sparing along with globally increased myocardial wall thickness (reflecting the presence of edema) without any late gadolinium enhancement. These findings were consistent with stress induced cardiomyopathy. Repeat examination two months after admission revealed complete normalization of left ventricular function, wall motion, and wall thickness and the absence of any late gadolinium enhancement.

Summary: Takotsubo cardiomyopathy rarely can be seen in normal healthy persons following consumption of EDs.

2.1.11. Aortic Dissection

The sympathetic surge and associated acute increase in blood pressure and heart rate associated with ED consumption described above is associated with precipitation of aortic dissection in those with an underlying predisposition [1,68].

A 48-year-old male with no past medical history reported severe chest pain starting 3 h prior to presentation [69]. He reported consuming two EDs just before the incident. On examination, his blood pressure was 145/95 mmHg. Echocardiography confirmed acute aortic dissection (De Bakey type I), He proceeded to surgery which was performed successfully and without complications.

A 54 year-old male with a history of hypertension and obesity presented with chest pain and shortness of breath starting five days prior to admission [69]. He reported consuming 4–5 EDs per night while driving his truck. His blood pressure was 190/110 and heart rate 110 bpm. Echocardiography and CT Chest confirmed a De Bakey Type I aortic dissection. He too underwent successful surgical repair.

A 26 year-old male with a history of a bicuspid aortic valve and dilation of the ascending aorta (5.0 cm) who was scheduled for elective surgery presented with chest pain of 5 h duration [69]. The pain started after a party where he consumed 5–6 EDs. He was noted to have mildly elevated systolic blood pressure of 145 mm Hg. Echocardiography and CT scan confirmed De Bakey Type II aortic dissection. Surgery was successfully performed on the aortic root and aortic valve.

It is important to note that patients with weakness of the aortic media (such as those with bicuspid aortic valves or Marfan syndrome) or other underlying cardiovascular diseases are more likely to have acute aortic dissection. These patients are particularly susceptible to complications arising from sudden changes in cardiovascular hemodynamics or increased shear stress [70]. Several of the cases above had a clear predisposition, yet one did not. Importantly, in all of these cases, the ruptures were preceded by the consumption of significant amounts of EDs (roughly 400 mg of caffeine and 5000 mg of taurine), thereby suggesting that the ED may have caused acute elevations in heart rate, blood pressure, and cardiac contractility. This in turn may have increased the hemodynamic stress load resulting in an acute aortic dissections.

Summary: Aortic dissection (DeBakey Types I and II) can be precipitated in those with or without known risk factors for aortic dissection (e.g., presence of a dilated ascending aorta) following consumption of EDs.

2.1.12. Postural Orthostatic Tachycardia Syndrome (POTS)

Taurine and caffeine are the ingredients of EDs that can directly or indirectly affect cardiovascular functions [71]. In particular taurine, a nonessential amino acid found in high concentrations in the brain, has the potential to interfere with cardiovascular regulation in experimental animals and in humans [40,72–75].

A 16 year-old female professional volleyball player gave a 3-month history of orthostatic intolerance and episodes of transient loss of consciousness [71]. She reported that one week prior to the onset of her orthostatic symptoms she started drinking 4–5 cans of Red Bull® ED a day. Her neurological and cardiovascular workup was suggestive of POTS, a type of orthostatic incompetence. She had a positive tilt table test, defined as lightheadedness or fainting accompanied by a rapid increase in heartbeat of more than 30 beats per minute or a heart rate that exceeds 120 beats per minute within 10 min of rising [76]. Her clinical symptoms resolved within one week of discontinuation of ED consumption. Autonomic tests repeated one month later were normal and she reported that the orthostatic intolerance had disappeared.

Summary: Postural orthostatic tachycardia syndrome can be rarely seen in normal healthy athletes following chronic consumption of 4–5 cans/day of EDs.

2.1.13. Sudden Cardiac Death

There is an increasing body of published case reports describing sudden cardiac death triggered by ED use in conjunction with exercise [10]. There is biological plausibility for sudden death, given that caffeine use during exercise reduces coronary artery flow reserve and increases myocardial oxygen demand [8]. The consumption of one or more EDs prior to exercise can accordingly decrease myocardial oxygen supply while the body enters a state of increased demand, thereby causing a classic supply-demand mismatch. This in turn results in myocardial ischemia (reduced oxygen supply to the heart muscle) and can result in ventricular arrhythmias and cardiovascular collapse [7,8,59,77,78].

The FDA's Center for Food Safety and Applied Nutrition Adverse Event Reporting System Voluntary and Mandatory Reports on 5-h Energy, Red Bull® ED, Monster Energy, and Rockstar (Rockstar Inc., Las Vegas, NV, USA) ED 1 January 2004, through 23 October 2012 reported 18 deaths in individuals related to consumption of these energy products [79]. Some examples include:

- A 14 year-old girl, in Hagerstown, MD, who died after drinking two, 24-ounce Monster EDs in 24 h; an autopsy concluded she died of cardiac arrhythmia due to caffeine toxicity [80].
- A healthy 18 year-old man, died while playing basketball after drinking two cans of Red Bull® ED [81].
- A healthy 16- year-old girl, an athletic teenage softball player, died after consuming several Red Bull® EDs [82]. The beverages were consumed while at the beach; later that day she reported malaise and shortness of breath. She was rushed to a hospital and was pronounced dead after suffering cardiac arrest.

In many cases, confounding variables in addition to ED consumption are present. These include co-ingestions (e.g., drugs), genetic predispositions, and strenuous exercise. Accordingly, specific causality cannot be attributed to ED consumption alone [1,83–85]. However in light of these patterns,

individuals susceptible to the effects of EDs avoid consumption until more safety and efficacy data can be established [1].

Summary: Sudden cardiac death is associated with consumption of EDs in normal young healthy persons or in those with underlying heart disease, following consumption of EDs.

2.1.14. Endothelial Dysfunction

Endothelial cells form the inner lining of blood vessels and have basal and inducible metabolic/synthetic functions which allow them to carry out multiple important tasks [86]. Normal endothelial cell function is important in regulating vascular resistance (vessel tone and variation), blood clotting, growth of nearby muscle cells, as well as providing a barrier function [87]. Normal endothelial function is promoted by exercise and a healthy diet, in addition to avoiding exposures known to be detrimental to endothelial function [87,88]. Abnormal endothelial cell function termed "endothelial dysfunction" is associated with vasoconstriction, poor vascular reactivity, pro-thrombosis, pro-adhesion, pro-inflammation, and growth promotion [89]. In addition, chronic endothelial dysfunction is associated with coronary artery disease, cerebrovascular disease, and peripheral arterial disease [89].

The high levels of caffeine and caffeine-like substances in ED may affect endothelial function [7]. In addition, it has been shown that caffeine in conjunction with exercise may result in endothelial dysfunction [8].

In the short term, endothelial dysfunction manifesting as an impaired ability to dilate the coronary arteries can reduce coronary blood flow and oxygen delivery [90,91]. Following exposure to stress, (including exposure to cold, mental arithmetic, anger, ingestion of a meal, or exercise, as well as cigarette smoking, cocaine, alcohol), the impaired ability to dilate the coronary arteries can result in supply–demand imbalance or coronary spasm, potentially leading to myocardial ischemia and/or cardiac arrhythmias such as ventricular tachycardia/fibrillation [92].

One study involving 50 healthy young adults (34 male, mean age 22 years) demonstrated an acute increase in platelet aggregation and decreased endothelial function 1 h following the consumption of 250 mL of sugar-free ED [78].

Another study of 11 healthy medical students (9 males, average age 24.5 years, average BMI 22.8 kg/m^2), underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow-mediated dilatation [77]. The subjects then drank a 24-oz can of Monster ED and the above was repeated at 90 min after consumption. Consumption of the ED resulted in a significantly attenuated peak flow-mediated dilatation response (mean ± SD): BL group 5.9% ± 4.6% *vs.* ED group 1.9% ± 2.1%; $p = 0.03$. Thus acute exposure to an ED was shown to impair arterial endothelial function in healthy young adults.

A 47 year-old healthy Caucasian male underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow-mediated dilatation [93]. He then drank a 24-oz Monster energy beverage in approximately 1 min. There was a progressive attenuation of peak flow-mediated dilatation response ninety minutes later, with a peak reduction of about 4% at 90 min.

Thus, it appears that acute exposure to an energy beverage impairs arterial endothelial function in healthy young adults. It is possible that such acute effects on endothelial function may play a role in

morbidity with concomitant ED intake and exercise, as there is an increased use of these beverages while exercising in young adults.

Summary: Consumption of an ED will acutely impair endothelial function in young healthy adults.

2.2. Chronic Effects

Since EDs have only recently become widely used, no significant research is available on the chronic effects of ED consumption in youth and adults. However, given the above acute effects, one could postulate long-term effects. For example, chronic daily elevations of blood pressure over years may lead to hypertension and hypertensive changes in the heart, which predisposes to coronary artery disease and arrhythmia. Furthermore, atherosclerosis occurs in the subendothelial space (intima) of medium-sized arteries at regions of disturbed blood flow and is triggered by an interplay between endothelial dysfunction and subendothelial lipoprotein retention [94]. Therefore chronic endothelial dysfunction from chronic ED consumption may predispose users to coronary artery disease, cerebrovascular disease, and peripheral arterial disease. At least one case of accelerated atherosclerosis was seen in a low-risk 26 year-old Hispanic male with chronic and excessive consumption of EDs [66].

Given to the dearth of information on the topic, further research is needed establish the safety of long-term ED consumption.

3. Suggestions

It is clear that ED consumption is associated with adverse cardiovascular events including death in both youth and adults [10,30,79]. As described above, there are some clear instances where ED consumption by adults should be avoided; one notable example is a patient with underlying QTc prolongation or one using potentiating medications [95]. At the very least, providers should obtain a baseline electrocardiogram and inquire about ED consumption to evaluate the risk of QTc prolongation in patients before prescribing medications implicated in cardiac abnormalities.

What is particularly concerning is that while some individuals have a clear underlying cardiac condition that increases the risk of adverse cardiac events, others do not. A recent review of the published cases of adverse cardiac events after ED ingestion noted that 15 of the 17 cases (88.2%) occurred in persons <30 years of age and that cardiac investigations did not reveal any predisposing cardiac abnormality in the majority of cases [10]. It is clear from this data that many of the adverse cardiac outcomes occur in young and otherwise healthy persons.

Based on our review, our suggestions regarding ED consumption are summarized in Table 2.

Given the high volume of ED sales (1.5 billion cans of Red Bull® ED were sold in the United States alone in 2011) it is likely that the overall risk of a major cardiovascular event is small [12]. However, such adverse events are also likely to be underreported because obtaining a history of ED use or testing for caffeine levels are not routinely performed during medical evaluations [10]. In a 2012 FDA report, 18 deaths and one nonfatal myocardial infarction were associated with consumption of EDs [79]. The FDA's reporting system is estimated to capture between 1% and 10% of the true adverse events associated with such supplements, so it can be inferred that 180 or more actual deaths related to ED consumption occurred [96].

Table 2. Suggestions for energy drink consumption.

Age and medical condition	Recommendation
<18 years old	Do not consume EDs
≥18 years old–healthy, non-pregnant, and taking no medications	No more than 1 regular can of ED per day at rest (avoid if any symptoms related to consumption) Do not consume ED prior to exercise Do not consume ED with alcohol
≥18 years old and pregnant	Do not consume EDs
≥18 years old and caffeine sensitivity	Do not consume EDs
≥18 years old and history of cardiovascular condition: Elevated blood pressure, Increased heart rate, Increased QTc interval, Supraventricular arrhythmia, Ventricular arrhythmia, Coronary artery spasm, Coronary artery thrombosis, Takasubu cardiomyopathy, ST-Segment Elevation Myocardial Infarction (STEMI), Sudden cardiac death, or Endothelial dysfunction	Do not consume EDs
≥18 years old and any other medical condition/taking medications	Do not consume EDs and discuss with health care provider

Considering the difficulty of determining true event rates, serious consideration should be given to building a nationwide and/or worldwide registry for adverse outcomes associated with ED consumption. The risk of consuming EDs in those with underlying structural heart disease and the general population should be more carefully studied [56]. Physicians should routinely inquire about ED consumption in relevant cases and vulnerable consumers such as young persons should be advised against heavy consumption, especially with concomitant alcohol or drug ingestion [10].

Educational campaigns and legal restrictions on the sale of EDs in other countries were associated with decreasing calls to poison centers for ED toxicity and are therefore encouraged [30]. Warning labels should be required to inform consumers of the risks posed by these drinks as well as appropriate limits for consumption [56].

Children, young adults, and their parents should be aware of the potential hazards of EDs [5]. Claims of boosting energy, physical performance, and cognitive performance have not been supported by rigorous scientific evidence [12,97–100]. Especially concerning is the observed association between ED consumption, poor mental health, and substance abuse behavior (cigarette, marijuana, alcohol, and illicit drug use) [101]. Indeed, EDs may be a gateway to more concerning behaviors and detrimental substances [102].

In 2007, the American Institute of Medicine recommended prohibition of ED use for children and adolescents [103]. In 2013, an American Institute of Medicine workshop noted that, while caffeine is among the most heavily studied food ingredients, "a wealth of unanswered questions remains about exposure to caffeine in food and dietary supplements and the health consequences of that exposure especially in certain potentially vulnerable populations", namely children and adolescents [104].

To date, for healthy adults FDA has cited 400 mg a day as a safe consumption limit; however, they have not set a level of safe consumption of caffeine for younger people.

In 2013, the International Sport Society stated that EDs contain many ingredients which need further studies to demonstrate their safety and potential harmful effects. They therefore recommended that children and adolescents should not consume EDs without parental permission [105].

In 2013, Health Canada stipulated that the daily caffeine intake for younger children should not be greater than 2.5 mg/kg of body weight [106]. Thus, EDs are not recommended.

As a society, we need to consider legislation to re-label these products as "foods and beverages" instead of "dietary supplements" so they are subject to higher FDA standards of safety and efficacy. Ideally this would lead to the eventual limitation of the caffeine content in EDs, restriction of sales to young persons, and clear labelling of contents with appropriate warnings for at-risk populations.

4. Conclusions

Monster Energy Drink operates under a campaign slogan of "Unleash the Beast". By "unleashing" the new "beast" of EDs, we have now seen significant morbidity and mortality in susceptible patients. With respect to the cardiovascular system, consumption of EDs is associated with increased demand of the heart via increased sympathetic tone, blood pressure, inotropy, and arrhythmias. There also may be concurrently reduced coronary artery blood supply via endothelial dysfunction, platelet aggregation, coronary thrombosis, and coronary spasm. Acutely, these changes to the cardiovascular system are associated with complications not only patients with underlying cardiovascular conditions but also in young people. These young consumers are at a particularly high risk of complications due to hazardous consumption patterns including frequent and heavy use. While the acute cardiovascular consequences of consuming EDs have been described, chronic cardiovascular consequences are less clear and more research is needed. Given the rise of emergency room visits for complications of ED consumption and also multiple reported deaths correlated with use, increased research to identify possible mechanisms of harm is absolutely necessary.

Author Contributions

Authors contributed equally to effort and content of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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