



Energy Drinks: Cardiovascular Complications

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Abstract

Energy drinks (EDs) are gaining popularity every year with a broad consumer base including athletes, amateur competitors, and office workers trying to avoid afternoon fatigue. Evidence suggests an association between ED consumption and adverse effects, especially in at-risk populations including those of young age, the caffeine-naive/sensitive, women, competitive athletes, and those with underlying cardiovascular disease. This paper summarizes the cardiovascular complications associated with ED use and provides suggestions on the consumption of these drinks in various populations.

Keywords: Energy Drinks; Endothelial Function; Heart; Cardiovascular Complications; Caffeine; Myocardial Infarction; Arrhythmia; QTc Interval

Introduction

Energy Drinks (EDs) are caffeinated beverages that are marketed to improve energy, athletic performance, concentration, endurance, and weight loss [1-5]. The consumption of EDs has increased significantly in recent years, with a growing market that is estimated to reach \$61 billion by 2021 worldwide [6]. It is important to recognize the difference between EDs and traditional soft drinks such as sodas, as well as coffee, tea, sports drinks (such as Gatorade), juices, or flavored water [7,8]. Some believe that "Energy drinks are the Wild West of the soft drinks industry: often shockingly and unnecessarily high in sugar and caffeine..." [9]. EDs typically contain taurine (an amino acid), niacin, pyridoxine, cyanocobalamin (B12), riboflavin (B2), ginseng extract, glucuronolactone (a glucose metabolite), inositol (B8), guarana (contains caffeine, theobromine, and theophylline), ephedra, yohimbine, Ginkgo biloba, kola nut, theophylline, sugars, vitamins, herbs, and L-carnitine [10]. Caffeine has even been added to foods too, and examples of foods and beverages caffeine content are freely available [11,12].

A typical ED contains 0.34 mg of caffeine per mL, which exceeds 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 [2,11,12]. Some EDs do not disclose total caffeine, as they may fail to account for the caffeine, contributed by "energy blend" ingredients (guarana, kola nut, yerba mate) [13,14]. While most healthy adults can safely consume up to 400 mg per day, other groups should be cautious [11]. Pregnant women should limit ED use to 200 mg per day, while adolescent adolescents and children should completely avoid consumption due to unknown risk profiles [15-18]. Despite the risk, consumption of EDs is highest among adolescents/young students and declines with increasing age [15]. EDs are now consumed by 30%-50% of adolescents, with 31% of 12-19-year-olds reporting regular use [2,17]. Up to 78% of young adults and students are consuming EDs on a weekly basis [19,20].

In a recent meta-analysis, adverse effects of EDs were common [21]. Frequently reported adverse events in the pediatric population were insomnia (35%), stress (35%), and depressive mood (23%). Frequently reported adverse events

in the adult population were insomnia (25%), jitteriness/restlessness/shaking hands (30%), and gastrointestinal upset (22%). ED consumption has been significantly associated with lower breakfast frequency, higher sugar-sweetened soda intake, video game use, unhealthy dietary and weight-control behaviors, insomnia, and later substance use [19,22,23]. ED consumption is associated with adolescent use of alcohol, tobacco, cannabis, prescription stimulants, and analgesics [24]. Alcoholic beverages prepared with EDs are popular amongst adolescents and college students and associated with smoking and illicit drug use [25-28]. Harmful consequences include automobile fatalities and increased rates of sexual abuse. [29-31]. Moreover, alcohol consumption can increase the half-life of caffeine by up to 72%, which may potentiate the ED exposure effects [32]. Combining energy drinks with alcohol also precipitates adverse cardiovascular events, posing a risk to the health of children and adolescents [33]. Emergency department visits related to complications of ED consumption are increasing in frequency, whether for toxicity or simply exposure-related, including young children [34-36]. Consumption of EDs has

been associated with exacerbation of underlying medical conditions too [2,36-40].

Cardiovascular complications associated with EDs include increased cardiometabolic risk with high intake of sugar, short-term blood pressure increases and a decrease in cerebral blood flow due to the caffeine content, increased or decreased blood pressure from taurine, unmasked cardiac conditions, such as channelopathies, and atrial and ventral arrhythmias [33]. Cardiovascular complications can also arise when EDs are mixed with stimulants, amiodarone, potent CYP1A2 inhibitors, warfarin, digoxin, or corticosteroids [33]. Adverse events associated with energy drinks may have a genetic predisposition [41]. This review will focus on ED complications involving the cardiovascular system.

Cardiovascular Complications

Cardiovascular complications of consuming EDs may be related to acute or chronic exposure [42,8]. These are listed in Table 1 and are detailed below.

Acute Effects

Acute Effects
Increased Blood Pressure (see Table 2)
Increased Heart Rate (see Table 3)
Increased Corrected QT (QTc) Interval (see Table 4)
Supraventricular Arrhythmia (see Table 5)
Ventricular Arrhythmia (see Table 6)
Coronary Artery Spasm (see Table 7)
Coronary Artery Thrombosis (see Table 8)
Spontaneous Coronary Artery Dissection (see Table 9)
Acute Coronary Syndrome (see Table 10)
Stress-Induced (Takotsubo) Cardiomyopathy
Aortic Dissection (see Table 11)
Postural Orthostatic Tachycardia Syndrome (POTS)
Sudden Cardiac Death (see Table 12)
Endothelial Dysfunction (see Table 13)
Possible Chronic Effects
Hypertension
Obesity
Coronary Artery Disease
Atherosclerosis
Cerebrovascular Disease
Peripheral Arterial Disease

Table 1: Cardiovascular complications associated with energy drinks (EDs).

Increased Blood Pressure: Numerous studies have associated EDs and their ingredients with acute hypertension (Table 2) [43,44]. Acute caffeine consumption can increase blood pressure and heart rate by increasing plasma renin, catecholamines, and dopamine [14,45]. In addition, synergistic effects between components of the “energy blend” used in EDs may also contribute, especially in children and hypertensive patients [1,43,46]. The effects of caffeine

on hemodynamics can last up to 5 h after ED ingestion. Such effects may be amplified by performing physical activity just after consumption [47-49].

- **Recap:** A typical increase in systolic and diastolic blood pressure in normal healthy persons 1-2 h following consumption of ED is approximately 4-9 mmHg and 1-6 mmHg respectively.

Authors (Ref)	Population	Energy Drink (ED)	Results
Grasser, et al. [43]	12 women	355 mL of Red Bull	SBP*: Increased by 5.2
			DBP*: Increased by 6.1
Steinke, et al. [50]	15 healthy 18-40 year olds	Two cans of 500 mL EDs	SBP: Increased by 7.2% and 9.6% DBP: Increased by 7.0% and 7.8%
Franks, et al. [51]	9 Subjects (5 females, mean age: 27.7)	Red Bull	SBP: Increased by 5.8 mmHg DBP: Increased by 5.4 mmHg
Elitok, et al. [44]	50 young, healthy subjects	Red Bull	SBP: Increased by 9 mmHg DBP: Increased by 3 mmHg
Peveler, et al. [52]	15 recreationally active men and women	1. Red Bull	SBP:
		2. Monster	1. Increased by 6.94 mmHg
		3.5 hour Energy	2. Increased by 9.54 mmHg
			3. Increased by 8.07 mmHg
			DBP:
			1. Increased by 0.67 mmHg
			2. Increased by 1.33 mmHg
	3. Increased by 1.33 mmHg		
Kozik, et al. [53]	14 healthy young subjects (mean age 28.6)	32 ounces of Monster energy drink	SBP: Increased by 18 mmHg
	38 adults (19 women, mean BMI 32 kg/m ² , mean age 22y)		
Basari, et al. [54]	38 adults (19 women, mean BMI 32 kg/m ² , mean age 22y)	3-4 cans of 250mL Red Bull	SBP: Increased by 3.8 mmHg
Nowak, et al. [55]	Young adults (average age 25 years; 49 female and 39 male participants)	600 mL of an unspecified ED	SBP: Increased by 5.6 mmHg
			DBP: Increased by 10.9 mmHg
Brothers, et al. [56]	15 participants	1.16 oz Monster Ed	SBP:
		2.24 oz of Monster ED	1. Decreased by 2 mmHg
		3. Coffee	2. Decreased by 2 mmHg
			3. No change in mmHg
			DBP:
			1. No change in mmHg
			2. No change in mmHg
	3. Increase in 1 mmHg		
Gray, et al. [57]	24 LQTS patients aged 16-50 years	2 Red bull sugar-free cans	SBP: Increased by 6mmHg
			DBP: Increased by 6mmHg
Shah, et al. [58]	Healthy volunteers between 18 and 40 years of age with no premorbid conditions were included	1 bottle (2 fl. Oz) of 5-hour Energy	SBP: Increased by 5mmHg
			DBP: Increased by 4 mmHg

Table 2: Increased blood pressure associated with energy drinks.

* SBP systolic blood pressure; DBP diastolic blood pressure

Increased Heart Rate: Acute consumption of EDs has been associated with small but significant increases in heart rate (Table 3).

- **Recap:** A typical increase in heart rate in normal healthy persons 1-2 h following consumption of ED is approximately 2-8 beats per minute.

Authors (Ref)	Population	Energy Drink (ED)	Results
Grasser, et al. [43]	25 young non-obese and healthy subjects	Red Bull	Increase in HR* relative to water control
Steinke, et al. [50]	15 healthy 18-40-year-olds	2-4 hours after ED consumption	Increase in HR by 7.8% and 11.0%
Elitok, et al. [44]	50 young, healthy subjects (mean age 25-year-old)	Red Bull	Increase in HR by 8 bpm
Nowak, et al. [55]	Young adults (average age 25 years; 49 female and 39 male participants) in Bydgoszcz, Poland	600 mL of an unspecified ED	Increase in HR by 3.8 bpm
Brothers, et al. [56]	15 healthy participants	1.16 oz Monster Ed	1. Increase in HR by 2bpm
		2.24 oz of Monster ED	2. Increase in HR by 4bpm
		3.Coffee	3.No change in HR

Table 3: Increased heart rate associated with energy drinks.

* HR heart rate

Increased Corrected QT (QTc) Interval: Possibly due to the effect of ingredients such as taurine on multiple cardiac ion channels, EDs have been associated with prolongation of the QT interval, although not all studies showed a significant

increase (Table 4) [59-61].

- **Recap:** A typical increase in heart rate in normal healthy persons 1-2 h following consumption of ED is approximately 4-8 milliseconds.

Authors (Ref)	Population	Energy Drink (ED)	Results
Steinke, et al. [50]	15 healthy 18-40 year olds	2-4 hours after ED consumption	Increase in QTc by 2.4% and 5.0%
Rottlaender, D. [62]	22 year old female with out of hospital cardiac arrest due to initial torsades de pointes tachycardia	Consumed six cans of caffeinated ED within 4 hours	Increased to 526 ms* from baseline 419
Dufendach, et al. [63]	13-year-old-girl with Type I Long QT Syndrome (LQTS)	Consumed one 16oz. can of an ED	Increased to 561 ms
Brothers, et al. [56]	15 healthy participants	1.16 oz Monster	1.Increased by 6ms
		2.24 oz Monster	2.Increased by 8ms
		3.Coffee	3. Increased by 4ms
Gray, et al. [57]	24 LQTS patients aged 16-50 years	Unspecified ED	Increased by 4ms
Shah, et al. [58]	Healthy volunteers between 18 and 40 years of age with no premorbid conditions were included	1 bottle (2 fl. Oz) of 5-hour Energy	Decreased by 2ms

Table 4: Increased Corrected QT (QTc) Interval associated with energy drinks.

* ms milliseconds

Supraventricular Arrhythmia: Consumption of EDs and other energy products has been associated with precipitation and/or exacerbation of supraventricular arrhythmia (Table 5) [17,64]. Atrial fibrillation, which is rare in the pediatric population, has been observed following acute ingestion of

EDs in young adults [65,66].

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

Authors (Ref)	Population	Energy Drink (ED)	Results
Izquierdo, et al. [67]	13-year-old healthy boy in Spain	Unspecified "EDs"	Atrial fibrillation with rapid ventricular response
Nagajothi, et al. [68]	23-year-old woman with no medical history	GNC Speed Shot (GNC Corporation, Pittsburgh, PA, USA) and a Mountain Dew (PepsiCo, Inc., Purchase, NY, USA) soda drink	Narrow Complex Tachycardia with Ventricular Rate of 219
Kaoukis, et al. [69]	24-year-old man	Unspecified ED	Supraventricular and Ventricular Tachycardia, Later Diagnosed as Takotsubo Cardiomyopathy
Peake, et al. [70]	58-year-old previously healthy male	One bottle (1000 mL) per week of a highly caffeinated (caffeine content 4.04 mg/mL) commercially available ED for six months	Atrial fibrillation with rapid ventricular response
Di Rocco, et al. [66]	Two Caucasian Adolescent Boys, aged 14 and 16, with no significant past medical history	One Can of Red Bull	Atrial Fibrillation
Mattioli, et al. [71]	22-year-old man, with a negative family, personal, and pharmacological history	750mL of ED	Atrial fibrillation with rapid ventricular response
Mattioli, et al. [71]	23 year-old-man, without previous cardiac disease or pharmacological treatment	600mL of ED	Atrial fibrillation with rapid ventricular response
Mattioli, et al. [71]	26- year-old-man, without any pharmacological, familiar and personal history	600mL of ED	Atrial fibrillation with rapid ventricular response

Table 5: Supraventricular Arrhythmia associated with energy drinks.

Ventricular Arrhythmia: Sudden cardiac death due to ventricular arrhythmias has been associated with ED use through means such as increasing catecholamines, electrolyte abnormalities inducing hypokalemia, or inactivation of sodium channels (Table 6) [13]. In addition, high doses of caffeine, like those found in EDs, may exacerbate cardiac conditions such as ion channelopathies and hypertrophic cardiomyopathy [2]. Taurine and guarana also have

proarrhythmic properties, making their consumption by patients with underlying structural heart disease potentially dangerous [72].

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

Authors (Ref)	Population	Energy Drink (ED)	Results
Avci, et al. [73]	28-year-old-man	Three cans of an ED	Ventricular Tachycardia
Cannon, et al. [74]	25-year-old woman with pre-existing mitral valve prolapse	55 mL of Race 2005 Energy Blast with Guarana and Ginseng	Ventricular Tachycardia
Berger, et al. [75]	28-year-old healthy man	7-8 cans of unspecified EDs	Intractable Ventricular Fibrillation
Rutledge, et al. [76]	24-year-old male with no previous medical history	Redbull ED	Ventricular Fibrillation
Goldfarb, et al. [77]	19-year-old man	Monster ED	Ventricular Fibrillation

Goldfarb, et al. [77]	57-year-old male	Multiple NOS ED	Cardiac Arrest
Kaoukis, et al. [69]	24-year-old	Unspecified ED	Supraventricular and Ventricular Tachycardia
Ward, et al. [72]	45-year-old man with a history of tetralogy of Fallot repair at age 5 and AICD placement at age 40	3 Red Bull EDs	Ventricular Tachycardia and Ventricular Fibrillation
Hanan Israelit, et al. [78]	24-year-old Caucasian man with a history of mild hypertension	20 cans of ED "XL"	Ventricular Fibrillation and Myocardial Infarction

Table 6: Ventricular Arrhythmia associated with energy drinks.

Coronary Artery Spasm: Consuming multiple cans of energy drinks with resultant high levels of caffeine (400-800 mg) as well as taurine (2000-8000 mg) has been associated with coronary artery vasospasm (Table 7). The mechanism is likely secondary to inhibition of adenosine A2 channels by caffeine [79,80]. However, taurine modulates calcium signaling and high levels can affect calcium concentration both intra- and extracellularly [14]. 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 [79,81].

- **Recap:** Coronary artery spasm may occur in normal healthy persons following consumption of multiple (2-8 cans) of EDs containing high levels of caffeine and taurine.

Authors (Ref)	Population	Energy Drink (ED)	Results
Scott, et al. [79]	19-year-old-man	2-3 Red Bull ED weekly	Coronary Artery Vasospasm
Berger, et al. [75]	28-year-old healthy man	7-8 cans of an unspecified ED	Coronary Artery Vasospasm
Wilson, et al. [82]	17-year-old male	3-4 Red Bull with 2-3 Monster	Coronary Artery Vasospasm

Table 7: Coronary Artery Spasm associated with energy drinks.

Coronary Artery Thrombosis: Coronary artery thrombosis has been associated with consumption of multiple (≥ 3 cans) EDs and sometimes in combination with alcohol (Table 8) [83,84].

- **Recap:** Coronary artery thrombosis may occur in normal healthy persons following consumption of multiple (3 or more cans) of EDs.

Authors (Ref)	Population	Energy Drink (ED)	Symptoms	Results
Benjo, et al. [83]	24-year-old African-American male	Three drinks of vodka mixed with an ED	Nausea, Emesis, Palpitations, Severe Retrosternal Chest Pain	Myocardial Infarction with Troponin I of 38 ng/mL
Unal, et al. [84]	32-year-old previously healthy man	Five bottles of energy drink	Retrosternal chest pain, palpitations, and emesis	Angiography demonstrated large thrombus occupying nearly 90% of L Main Coronary Artery

Table 8: Coronary Artery Thrombosis associated with energy drinks.

Spontaneous Coronary Artery Dissection: Spontaneous coronary artery dissection has been described in association with ED consumption in a 13-year-old and 25-year-old male, with likely excess consumption [85,86].

- **Recap:** Spontaneous coronary artery dissection may occur in normal healthy persons following consumption of multiple (3 or more cans) of EDs.

Authors (Ref)	Population	Energy Drink (ED)	Symptoms	Results
Solomin, et al. [85]	13-year-old male	Ingested an unknown ED	Acute-onset, "crushing", mid-sterna chest pain	ECG revealed sinus rhythm 2- to 3-mm ST-segment elevations in leads II, III, aVF, and V3 through V5
Zacher, et al. [86]	25-year-old male	Consumed "more than 8 cans" of EDs	Chest Pain, persistent vomiting,	ECG showed a sinus rhythm with ST-segment elevation in I, aVL, and V II, III, aVF, and V3 through V1-V4 and corresponding inferior ST-segment-depression

Table 9: Spontaneous Coronary Artery Dissection associated with energy drinks.

Acute Coronary Syndrome: Acute coronary syndrome in association with energy drink consumption has been described in young males, age 17-32 years old, with multiple cans of EDs typically being consumed [75,78,82,84,85,87]. Some required stenting, others were found to have thrombosis or spasm. The etiology may include high cardiovascular demand from excess caffeine, coronary vasospasm, endothelial dysfunction, and a temporary hypercoagulable state [8,42]. A notable example is was a 26-year-old Hispanic male with a 2-year history of smoking

presented with an acute ST-Elevation Myocardial Infarction (Table 10) [85]. 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.

- **Recap:** Acute coronary syndrome may occur in normal healthy persons following consumption of multiple (usually 3-5 or more cans) of EDs.

Authors (Ref)	Population	Energy Drink (ED)	Results
Solomin, et al. [85]	26-year-old male	Consumed 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
Wajih Ullah, et al. [87]	25-year-old male	Consumed "massive" quantities of energy drinks	Patient had an acute myocardial infarction, confirmed by ECG showing ST depression in precordial leads V2-V6
Berger, et al. [75]	19-year-old male	Consumed 2-3 cans of a "popular" ED in days leading up to event	ECG and Troponin value of 34.7 µg/ml confirmed diagnosis of a STEMI*
Hanan Israelit, et al. [78]	24-year-old male	Consumed 20 cans of an ED with 3,4-methylenedioxymethamphetamine (MDMA)	ECG revealed widespread ST elevations, confirming diagnosis of STEMI
Wilson, et al. [82]	17-year-old male	Consumed 5-7 cans of caffeinated ED	Cardiac biomarkers and ECG confirmed presence of STEMI
Unal, et al. [84]	32-year-old male	Consumed five bottles of ED	ECG showing ST elevations and coronary angiography showing thrombus occupying 90% of left main coronary artery

Table 10: Acute Coronary Syndrome associated with energy drinks.

* STEMI ST-segment elevation myocardial infarction.

Stress-Induced (Takotsubo) Cardiomyopathy: EDs contain sympathomimetic substances such as caffeine and others. 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 [11]. Caffeine also induces catecholamine release and causes a rise in intracellular calcium within myocytes, especially when consumed in massive amounts [11,81,88]. Such catecholamine surges can precipitate Stress-Induced (Takotsubo) Cardiomyopathy:

A 24-year-old man presented with palpitations, chest pain, and acute respiratory failure shortly after ingesting an ED [69]. Frequent runs of supraventricular and ventricular tachycardia were noted. His electrocardiogram showed sinus tachycardia and nonspecific T-wave inversion in leads I and aVL; echocardiogram, showed a reduced left ventricular ejection fraction of 35%, and a diagnosis of Stress-Induced (Takotsubo) Cardiomyopathy was made.

- **Recap:** Stress-Induced (Takotsubo) Cardiomyopathy rarely can be seen in normal healthy persons following consumption of EDs.

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 (Table 11) [1,8,89]. It is important to note that patients with underlying cardiovascular diseases are more likely to have acute aortic dissection, especially during conditions of changes in cardiovascular hemodynamics or increased shear stress [90]. Several of the cases described 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 aortic dissection may have been caused by the acute elevations in heart rate, blood pressure, and cardiac contractility from ED use.

- **Recap:** Aortic dissection (DeBakey 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 binge consumption of EDs.

Authors (Ref)	Population	Energy Drink (ED)	Results
Jonjev, et al. [91]	54-year-old Caucasian man with uncontrolled hypertension and obesity	4-5 Unspecified EDs	Acute Aortic Dissection (De Bakey Type I)
Jonjev, et al. [91]	26-year-old Caucasian man with history of bicuspid aortic valve	5-6 Unspecified EDs	Aortic Dissection (De Bakey Type II)
Jonjev, et al. [91]	48-year-old Caucasian man with history of hypertension and myocardial infarction	"Several" High Energy Drinks	Aortic Dissection (De Bakey Type I)

Table 11: Aortic Dissection associated with energy drinks.

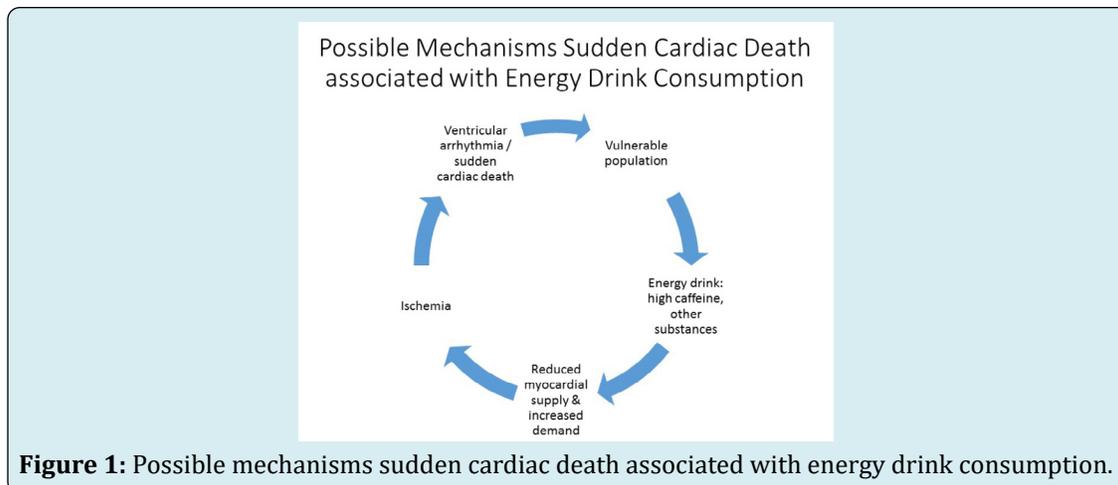
Postural Orthostatic Tachycardia Syndrome (POTS)

Taurine and caffeine are the ingredients of EDs that can directly or indirectly significantly affect cardiovascular function [92]. In particular taurine, a nonessential amino acid found in high concentrations in the brain, can interfere with cardiovascular regulation [49,93-96]. Such alterations can lead to Postural Orthostatic Tachycardia Syndrome (POTS). Once such case involved a 16-year-old female professional volleyball player who gave a 3-month history of orthostatic intolerance and episodes of transient loss of consciousness [92]. 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, combined with a positive tilt table test, was suggestive of POTS, a type of orthostatic incompetence [97]. Her clinical symptoms resolved within one week of discontinuation of ED consumption and confirmatory tests performed one month later were reportedly normal.

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

Sudden Cardiac Death

Case reports exist describing sudden cardiac death triggered by ED use in conjunction with exercise (Table 12) [13,8]. There is biological plausibility for sudden death, given that caffeine use during exercise reduces coronary artery flow reserve and increases myocardial oxygen demand [8,11]. These physiologic phenomena can be exacerbated by ED use because of the increased myocardial oxygen demand and reduced coronary flow that may follow their acute consumption [8,10,11,42,75,98,99,]. Thus, a proposed mechanism for sudden cardiac death associated with ED consumption is shown in Figure 1. 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 in 2012 reported 18 deaths in individuals related to consumption of these energy products [100]. 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, because specific causality cannot be attributed to ED consumption alone, at-risk individuals should avoid ED consumption [1,8,101-103].



- **Recap:** Sudden cardiac death is associated with consumption of EDs in normal young healthy persons or in those with underlying heart disease.

Authors (Ref)	Population	Energy Drink (ED)	Results
CFSAN Adverse Event Reporting System [104]	14-year-old girl	48 oz of Monster ED	Cardiac Arrhythmia
CFSAN Adverse Event Reporting System [105]	18-year-old man	2 cans of Red Bull ED	Sudden Death During Basketball
CFSAN Adverse Event Reporting System [106]	16-year-old girl	“Several” Red Bull Eds	Cardiac Arrest

Table 12: Sudden nm., Cardiac Death associated with energy drinks

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 in the vasculature and muscles [98, 99]. Normal endothelial function is promoted by exercise and a healthy diet [99,100].

The high levels of caffeine and caffeine-like substances in ED may adversely affect endothelial function, thus being associated with vasoconstriction, poor vascular reactivity,

coronary artery disease, cerebrovascular disease, and peripheral arterial disease (Table 13) [10,11,42,107].

In the short term, endothelial dysfunction manifesting as an impaired ability to dilate the coronary arteries may reduce coronary blood flow and oxygen delivery [108,109]. Following exposure to various environmental stressors, the impaired ability to dilate the coronary arteries could result in supply–demand imbalance or coronary spasm, potentially leading to myocardial ischemia and/or cardiac arrhythmias such as ventricular tachycardia/fibrillation [110].

Authors (Ref)	Population	Energy Drink (ED)	Results
Worthley, et al. [99]	50 healthy young adults	250mL of a sugar-free ED	an acute increase in platelet aggregation and decreased endothelial function
Higgins, et al. [98]	11 healthy medical students (9 males, average age 24.5 years, average BMI 22.8 kg/m ²)	24-oz can of Monster ED	Attenuated peak flow-mediated dilatation response (mean \pm SD): BL group 5.9% \pm 4.6% vs. ED group 1.9% \pm 2.1%; p = 0.03. Thus acute exposure to an ED was shown to impair arterial endothelial function in healthy young adults
Higgins, et al. [111]	47 year-old healthy Caucasian male	24-oz Monster energy	Progressive attenuation of peak flow-mediated dilatation response ninety minutes later, with a peak reduction of about 4% at 90 min
Higgins, et al. [42]	44 healthy medical students (34 males, average age 24.7 years, average BMI 23.4 kg/m ²)	24-oz can of Monster ED	Attenuated peak flow-mediated dilatation response (mean \pm SD): BL group 5.1% \pm 4.1% vs. ED group 2.8% \pm 3.8%; p = 0.004. Thus acute exposure to an ED was shown to impair arterial endothelial function in healthy young adults

Table 13: Endothelial Dysfunction associated with energy drinks.

- **Recap:** Reduced endothelial function is associated with consumption of EDs in normal young healthy persons.

Possible Chronic Effects

Despite little research in the long-term effects of EDs, chronic effects are plausible [8,42]. For example, chronic daily elevations of blood pressure over many years may lead to hypertensive changes in the heart and development of atherosclerosis, and an increase risk of acute coronary syndrome and stroke [112]. Chronic endothelial dysfunction from long-term ED consumption may predispose users

to coronary artery disease, cerebrovascular disease, and peripheral arterial disease. At least one case of accelerated atherosclerosis case was described in a 26-year-old Hispanic male with chronic and excessive consumption of EDs [85]. Given to the dearth of information on the topic, further research is needed establish the safety of long-term ED consumption.

- **Recap:** Chronic exposure to EDs may increase cardiovascular risk factors and translate into an increased incidence of premature cardiovascular disease.

EDs should not be consumed by children, adolescents, or pregnant women
EDs should not be used for hydration by children and adolescents, and information about the absence of benefit and potential adverse effects should be provided to their caregivers.
EDs should not be available in K-12 schools for sale, nor be advertised to children who attend such schools.
EDs may contain high levels of carbohydrates and calories, which can contribute to obesity.
EDs should not be marketed to nor consumed by vulnerable populations, including those younger than 18 years old, pregnant or breastfeeding women, caffeine naive or sensitive individuals, taking stimulant or caffeine-based medications, or those with certain cardiovascular or medical conditions, or taking medications known to interact with caffeine.
EDs should be avoided before, during, or after strenuous activities, until such time that proper safety and efficacy data are available.
EDs should avoided in patients with cardiovascular risk factors and cardiovascular conditions.
EDs should not be consumed close to bedtime.
ED manufacturers should not promote excessive or rapid consumption of their energy drink, as this 'binge' pattern has been associated with increased adverse events
Education about EDs and their potential adverse events should be encouraged, especially in schools and universities.
More research on the acute and chronic effects of EDs is needed to clarify who can safely consume them and what is a safe dose to consume.

Table 14: Recommendations regarding energy drinks (eds).

Recommendations

It is clear that ED consumption is associated with adverse cardiovascular events including death in both youth and adults [13,36,100]. However, the majority of ED-related cardiovascular events, however, occur in patients without any underlying cardiac condition [42,101]. 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 [13]. Underreporting of adverse effects of EDs is a widespread problem given that EDs are not usually screened for despite ED prevalence [13,113]. In a 2012 FDA report, 18 deaths and one nonfatal myocardial infarction were associated with consumption of EDs [100]. With a true event capture rate, it can be inferred that 180 or more actual deaths related to ED consumption occurred [114].

Considering the difficulty of determining true event rates, physician inquiries and public campaigns regarding the importance of limiting ED use are necessary [13,72].

The public should be aware of the potential hazards of EDs [7]. Their purported "benefits" have not been supported by rigorous scientific evidence [42,113-118]. Especially concerning is the observed association between ED consumption, poor mental health, and substance abuse behavior (cigarette, marijuana, alcohol, and illicit drug use) [42,119,120]. In 2007, the American Institute of Medicine recommended prohibition of ED use for children and adolescents [121]. In 2013, this group further recommended that while caffeine is among the most heavily studied food ingredients, there still remains many unanswered questions with respect to adolescent population [122].

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 whose safety is unknown. They therefore recommended that children and adolescents should not consume EDs without parental permission [123]. 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 [124]. Thus, EDs are not recommended. Re-labeling EDs to “foods and drinks” would subject these products to more FDA scrutiny. 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 [125-128]. Based on our review, our suggestions regarding ED consumption are summarized in Table 2.

Conclusion

Monster Energy Drink operates under a campaign slogan of “Unleash the Beast.” But at what cost? Indeed, by “unleashing” the new “beast” of EDs and/or excess consumption leading to high levels of caffeine, we have now seen significant adverse events, especially 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 are associated with complications in healthy persons and cardiac patients. While the acute cardiovascular consequences of consuming EDs have been described, chronic cardiovascular consequences are not well studied and more research is needed. For now, those vulnerable to their effects should avoid them, and others should wait until more research is available to determine the safety and efficacy of EDs.

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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