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REVIEWS

European Cardiac Arrhythmia Society Statement on the cardiovascular events associated with the use or abuse of energy drinks

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Abstract
Energy drinks are increasingly used by young people and young athletes in order to improve their performance alone or in association of other substances, particularly alcohol. In recent years, a number of reports of reports have raised attention on the side-effects associated with the use or abuse of energy drinks particularly serious cardiovascular events. The European Cardiac Arrhythmia Society (ECAS) has undertaken a systematic and critical review of reported data on cardiovascular events including life-threatening arrhythmias with or without cardiac arrest and other cardiovascular events, and discussed in this review the possible causal effect of caffeine and other ingredients contained in energy drinks and the reported events. Twenty-two cardiovascular events were reported in association with the use or abuse of energy drinks. The European Cardiac Arrhythmia Society would like to draw attention on the possible cardiovascular complications that may occur with the consumption of these beverages and to emphasize the prevention measures to be taken particularly in the young population. Well-designed prospective studies are needed to clarify the possible role of energy drinks in inducing the cardiovascular events reported.

Keywords ECAS statement · Position paper · Energy drinks · Cardiac arrest · Cardiovascular events · Caffeine intoxication · Taurine · Glucoronolactone · Guarana · Ginseng · Yerba mate

1 Introduction

The term "energy drinks" designates a group of non-alcoholic drinks which possess stimulating properties and are used to improve physical activity as well as cognitive functions; increase athletic performance, alertness, and concentration; and boost the energy. They should be differentiated from "energetic" drinks or "sports drinks" aimed at improving physical performance. The first energy drink was "Red Bull," introduced in Austria in 1987 and in the USA in 1997 [1]. The second

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energy drink marketed in the USA was "Monster" in 2002. In Canada, energy drinks were introduced in 2002. Several European Regulatory Authorities were reluctant to authorize energy drinks because of the high content in caffeine and the lack of scientific information regarding the other ingredients (e.g., taurine) [2]. Energy drinks were marketed in Germany in 1997 and approved in France in 2008 and are currently available in most European countries. In the USA, energy drinks are classified among the Dietary Supplements and as such do not require approval by the Food and Drug Administration [3].

Energy drinks are mainly used by young people (18–34 years) including students, adolescents, and young athletes in order to improve their performance [4–8]. Since 2011, a number of case reports and review articles [9–16] have raised attention on various risks related to the use or to the misuse of energy drinks, particularly cardiovascular events including the risk of cardiac arrest and sudden cardiac death [3, 12–16]. Furthermore, energy drinks are often used in combination with alcohol or illicit drugs which may potentiate their effects.

The European Cardiac Arrhythmia Society (ECAS) has undertaken a critical review of reported data on energy drinks particularly cardiovascular events and the possible relation cause to effect in order to issue recommendations on the safer use of these beverages.

2 Epidemiology

The use of energy drinks has experienced enormous growth both in the USA and in the 166 countries where they are marketed. In France, the market for energy drinks has shown a growth of 63% between 2006 and 2010 [2]. The growth of the market for energy drinks in the USA has exceeded 240% between 2004 and 2009 [17]. This is explained by more label initiatives, (come) multipack options, sugar-free versions, and juice hybrids that improve their flavor and also by creative advertisements as emphasized by Heckman et al. [17]. The target markets are teenagers and young adults (18–34 years old). It is estimated that energy drinks are consumed by 30 to 50% of the young population in the USA [9]. According to the Drug Abuse Warning network [18] (The DAWN Report), the number of the Emergency Department visits involving energy drinks because of side effects or because of the misuse or abuse doubled from 2007 to 2011 (10,068 to 20,783 visits). The patients aged 18–25 were most commonly involved in energy drink emergency visits.

In the USA, Red Bull® has 42.6% of the market, followed by Monster® (14.4%), Rockstar® (11.4%), Full Throtte® (Coca-Cola 6.9%), and Amp® (Pepsi-Cola, 3.6%) [19].

In a survey done in Italy among medical students during the academic year 2012–2013, 22% were regular users of energy drinks [20]. The users were younger (21 ± 1.9 years) than non-users. Alcohol consumption was more frequent particularly during the weekend among users of energy drinks than non-users. Forty-five percent of medical students declared side effects after consumption of energy drinks, mainly palpitations, insomnia, and irritability.

3 Main ingredients contained in energy drinks

Despite a large number of energy drink brands available, most of them share very similar ingredient composition. Caffeine and taurine are the main ingredients, present at various concentrations. Carbohydrates in various forms (glucose, sucrose, maltodextrin…) are also used as a source of rapid energy, even if sugar-free options are available as well. Other ingredients commonly found in energy drinks are niacin, pyridoxine, cyanocobalamin (B_{12}), riboflavin (B_2), ginseng, inositol (B_8), ephedra, yohimbine, *Ginkgo biloba*, kola nut, L-carnitine, guarana, yerba mate, and green tea extracts [17, 21]. The specific combination of these different ingredients is crucial because it determines the amount of energy and constitutes the claimed properties of the beverage. It is important to note that while caffeine concentrations vary among different beverages, all energy drinks contain caffeine concentrations higher than those of usual soft drinks (Table 1). Moreover, some energy drinks do not include in their composition the disclosed caffeine content, the caffeine amount provided by "energy blend" ingredients such as guarana, kola nut, and yerba mate [10, 17]. The ingredients other than caffeine that may be contained in energy drinks are shown in Table 2.

Table 1 Content of caffeine in food/drink/drug. Amount of caffeine is intended per service if not indicated otherwise

Item	Average amount of caffeine
10 Hour Energy Shot	420 mg
5 Hour Energy ED	200 mg
Caffeine pill	200 mg
Monster® ED	160 mg
Americano coffee	150 mg
Starbucks® Doubleshot	125 mg
Red Bull® ED	80 mg
Espresso coffee	80 mg
Instant coffee	60 mg
Iced tea	45 mg
Coke®	40 mg
Milk chocolate (60 g)	30 mg
Green tea	25 mg
Chocolate mousse (90 g)	15 mg
Decaffeinated coffee	5 mg

ED, energy drink

Table 2 Substances other than caffeine contained in energy drinks

Ingredient	Biological role
Glucuronolactone	Derivative of glucose which regulates glycogen formation
Guarana	Contains xanthine alkaloids, like theobromine and theophylline. It has also bioactive properties including antioxidant activity due to relatively high amounts of saponins, flavonoids and tannin
Taurine	Nonessential amino acid fundamental for conjugation of bile acids, antioxidation, osmoregulation, membrane stabilization and modulation of calcium signaling
Ginseng	Ginseng's active constituents, ginsenosides, have proved to have several beneficial properties such as being an immune stimulant, improving physical and mental conditions, and an anti-stress, antiaging, antioxidant, and anti-inflammatory action
Yerba mate	Yerba mate has anti-inflammatory, antidiabetic and antioxidant properties. Furthermore, yerba mate has a high caffeine concentration, which is responsible of its stimulant action on central nervous system
B vitamins	Vitamin B_2 is a coenzyme in the metabolism of carbohydrates. Vitamin B_3 acts as a coenzyme in energy metabolism and fat synthesis. Vitamin B_6 is a group of 3 structurally similar compounds that all can be converted into the vitamin B_6 coenzyme which aids in the utilization of carbohydrates, fats, and proteins. Finally, vitamin B_{12} is involved in folate metabolism and in nerve function

4 Cardiovascular effects of high doses of caffeine

Caffeine has several effects on the cardiovascular system. The main pharmacodynamic effects of caffeine at cellular level are competitive blockade of A_1 and A_{2A} adenosine receptors and consequent increase in the release of dopamine, noradrenaline, and glutamate [22, 23]. Adenosine acts through specific receptors and has a negative inotropic and chronotropic effects. The blockade of cardiac adenosine receptors inhibits adenosine effects resulting in increased heart rate and blood pressure and possibly in cardiac arrhythmias. At higher doses, caffeine induces also phosphodiesterase inhibition interacting with the sympathetic nervous system and inducing β_1-receptor stimulation. The final effect is a positive inotropic and chronotropic effect. This pathway leads to an increase in intracellular cAMP and cGMP and intracellular calcium overload. The latter mechanism may increase the susceptibility for arrhythmia occurrence. Animal studies [24] support proarrhythmic effects of high doses of caffeine, an evaluation based on invasive techniques. Increasing doses of caffeine (1–5 mg/kg) were given to dogs and resulted in increased incidence of both supraventricular and ventricular arrhythmias [25]. Nonetheless, there are some other animal studies [26] that have shown no effect or a favorable effect of caffeine on the inducibility of arrhythmias.

Human epidemiological studies investigating the issue of caffeine-induced cardiac arrhythmias have given conflicting results [27–30]. The electrophysiologic properties of caffeine have been reported by Dobmeyer et al. [27] in 7 normal volunteers and in 12 patients in whom 7 had a mitral valve prolapse syndrome before and after 200 mg of caffeine orally or 200 mg of caffeine citrate intravenously. The conduction time intervals of the right atrium, the AV node, or His-Purkinje system did not change. However, the effective refractory period (ERP) of the AV node and the right ventricle shortened whereas the ERP of the left atrium lengthened. Two patients had non-sustained ventricular tachycardia and 2 of the control patients had atrial-flutter fibrillation only after administration of caffeine. In another study, administration of caffeine (1 mg/kg per 24 h) in patients with baseline frequent premature ventricle contractions (PVCs) resulted in 50% increase in PVCs whereas the control group did not show PVCs [31]. In a randomized, double-blind study, a 300-mg dose of caffeine was given to patients within 7 days of acute myocardial infarction which resulted in an increase in epinephrine level and in systolic blood pressure but without any increase in frequency or severity of ventricular arrhythmias in this high-risk group of patients [32]. Similarly, in a subsequent study, administration of higher dose of caffeine (450 mg) to patients with recent myocardial infarction showed no increase in ventricular ectopy or arrhythmias detected with 24-h ECG monitoring [33]. Chelsky et al. [34] performed invasive electrophysiology in patients with known symptomatic non-sustained ventricular arrhythmias 1 h before and 1 h after caffeine ingestion. Caffeine did not significantly alter inducibility or severity of arrhythmias, suggesting that caffeine has little effect on the substrate generating ventricular arrhythmias. Notably, the magnitude of increase in circulating epinephrine level due to caffeine ingestion is sixfold less than the increase noted during exercise alone. Prineas et al. [35] in a survey of 7311 healthy patients revealed that drinking 9 or more cups of coffee per day was associated with twice the risk of PVCs after adjusting for other risk factors. A recent meta-analysis demonstrates that while caffeine seems to reduce ventricular fibrillation threshold in animal studies, data from human interventional studies do not show a significant effect of caffeine consumption on the occurrence of PVCs. [36]

As caffeine promotes direct vasoconstriction and increment of circulating catecholamines, a potential role on cardiac ischemia has been suggested based on case reports [14]. In patients with known coronary artery disease (CAD), caffeine

at a dose of 250 mg showed no effect on exercise duration, time to onset of angina, and time to onset of ST segment depression at exercise stress test, although peak blood pressure increased by 7 mmHg. [37] On another study, Namdar et al. [38] found that 200 mg of caffeine reduced myocardial blood flow during bicycle stress test both in patients with CAD and in normal subjects.

5 Effects of single dose of caffeine consumption (shot)

Reviewed scientific evidences and previous safety consensus on caffeine consider a dose of caffeine up to 200 mg (about 3 mg/kg for a 70-kg adult) from all sources as safe and with no health concerns for the general healthy adult population. However, caffeine consumption of 500 mg per day considered safe in adults may not be safe in adolescents 12–17 years old, an amount easily achieved with few cans of certain energy drinks [12, 39].

Once ingested, caffeine is quickly absorbed from the gastrointestinal tract into the circulatory system with a maximum plasma concentration after 30–60 min. Inter-individual differences and association with food may haste or delay peak plasma concentration. The pre-systemic (first-pass) metabolism that takes place in the liver through the portal circulation is negligible and, once caffeine is absorbed, it is promptly distributed through the body and crosses the blood-brain, blood-placenta, and blood-testis barrier [23]. Renal excretion of caffeine is < 2% with liver metabolism which accounts for about 95% of caffeine clearance. With higher levels of intake, a prolonged duration of action can be observed, possibly because of an accumulation of its metabolites: the chemical structure of the xanthines (paraxanthine, theobromine, and theophylline) is very similar to that of caffeine. These metabolites are further transformed in the liver resulting in the production of urates. Caffeine half-life in humans ranges from a minimum of 2 to a maximum of 12 h, mainly due to the inter-individual variability in absorption and metabolism [22]. Lethal dose of caffeine has been studied on animals and is over 200 mg/kg [39] (70–100 cups of coffee for adult human). Each of caffeine metabolites is further metabolized and then excreted in the urine. Nawrot et al. [28] showed that among the healthy adult population, a moderate daily caffeine intake of ≤ 400 mg (equivalent to 6 mg/kg/day for a 65-kg person) was not associated with any adverse effects. The average caffeine content of an energy drink typically ranges from 83 to 140 mg/8 oz (226 mL), which is significantly below this 400-mg per day limit and is comparable to consuming 5 oz (141 mg) of coffee or 2 cans of a caffeinated soft drink [4]. However, it is important to be aware of the total amount of caffeine dosage present in one can, since many of the 16-oz containers actually hold 2 servings. Moreover, consumers, especially young ones, often drink more than one can within a short period of time. Nonetheless, caffeine has a long history of safe use and overwhelming scientific evidence that when consumed in moderation (300 to 400 mg/day/adult) is not associated with adverse effects. However, it is also important to keep in mind that the FDA consumer report states that no safe levels of caffeine consumption have been determined in children as already mentioned. [9] Much like other psychoactive drugs, caffeine displays some aspects of dependence and exhibits tolerance and perhaps withdrawal.

6 Taurine

Taurine, or 2-aminoethanesulfonic acid, is an organic acid widely distributed in animal tissues, primarily in the retina and skeletal and cardiac muscle tissue [40, 41]. It is a major constituent of bile and can be found in the large intestine. Taurine is derived from the metabolism of methionine and cysteine [42, 43] and has many fundamental biological roles, such as conjugation of bile acids, antioxidation, osmoregulation, membrane stabilization, and modulation of calcium signaling. Taurine is found naturally in fish and meat. The mean daily intake from omnivore diets was determined to be around 58 mg (range from 9 to 372 mg) and to be low or negligible from a strict vegan diet. In another study, taurine intake was estimated to be generally less than 200 mg/day, even in individuals eating a high-meat diet [44]. Energy drinks contain synthetic taurine in very large concentrations. Taurine analysis of 80 different energy drinks showed an average concentration of 3180 mg/L, which is equivalent to 753 mg/8 oz. [45] Currently, no minimum level of intake with adverse effect has been defined for taurine, but a recent risk assessment study found the upper level of taurine supplementation to be 3 g per day. This assessment was based on toxicological evidence from a review of all human clinical trials with taurine supplementation [44]. Although taurine is likely to be safe in small doses, concern has been raised on the effects of large quantities of taurine in combination with other ingredients commonly found in energy drinks. Further studies are needed to clarify the effects of high doses of taurine consumption.

7 Glucuronolactone

Glucuronic acid exists both as a free acid and as a lactone. It is a derivative of glucose which regulates glycogen formation. The daily natural input of glucuronolactone is 1–2 mg/day. A can of Red Bull® for example contains 600 mg. The effects of such massive doses on human health are still unknown and the claim that it improves concentration and memory has not been demonstrated.

8 Guarana

Guarana comes from the *Paullinia cupana*, which is a climbing plant in the maple family, Sapindaceae, native to the Amazon basin and particularly common in Brazil. The plant produces small-berry like fruit, which contains 1 to 3 dark seeds, which are about the size of a coffee bean. The seeds contain about twice the concentration of caffeine than that found in coffee seeds (about 2–4.5% caffeine in guarana seeds compared with 1–2% for coffee seeds) with 1 g of guarana being equivalent to about 40-mg caffeine [46]. Guarana contains other xanthine alkaloids, like theobromine and theophylline, however, at much lower levels compared with caffeine [47]. Guarana has become an increasingly common natural additive in energy drinks mainly for its stimulatory effect, which is anyway slighter and featured by a slower action than pure caffeine [48]. Guarana has also bioactive properties including antioxidant activity due to relatively high amounts of saponins, flavonoids, and tannins. Guarana has shown to have no toxic effects neither in acute at high doses or in chronic at lower doses [49] but there is, however, no conclusive research that shows the caffeine release and absorption from guarana to be any different from that of pure caffeine [50].

9 Ginseng

Over centuries, ginseng has been considered in China an important component of Chinese traditional medicine as a remedy for various diseases and for promoting longevity [51]. *Panax ginseng* is the primary commercial species and belongs to the plant family Araliacae. Ginseng's active constituents, ginsenosides, have proved to have several beneficial properties such as being an immune stimulant, improving physical and mental conditions, and being an anti-stress, antiaging, antioxidant, and anti-inflammatory action [52]. Each ginsenoside has its own unique structure; therefore, various pharmacological effects can result [53]. A consistent amount of data concerning the effects of Ginseng on animals and humans indicate that ginseng may be considered as safe. However, few reports show that very high doses of ginseng may be associated with side effects. Finally, despite the significant number of studies of current literature, there is a lack of evidence concerning the real effect of ginseng on physical performance, psychomotor performance, and cognitive function [53, 54].

10 Yerba mate

Yerba mate is a species of the holly family (Aquifoliaceae), with the botanical name *Ilex paraguariensis*, native to South America. It is widely known as the source of the tea called mate, which since many centuries has largely been consumed in South American countries [55]. The increasing yerba mate popularity is due to its bioactive components including polyphenols, xanthine, flavonoids, saponins, amino acids, minerals, and vitamins. Yerba mate has anti-inflammatory, antidiabetic, and antioxidant properties [56]. Furthermore, yerba mate has a high caffeine concentration, which is responsible for its stimulant action on the central nervous system and which also represents the primary reason for incorporating yerba mate into energy drink formulations. In fact, 1 cup (8 oz or 236 mL) of yerba mate tea contains around 78 mg of caffeine which is close to the 80 mg already present in 8 oz of Red Bull®.

11 B vitamins

Vitamins B_2 (riboflavin), B_3 (niacin), B_6 (pyridoxine, pyridoxal, pyridoxamine), and B_{12} are those most commonly incorporated into energy drink formulation. Vitamin B_2 is a coenzyme in the metabolism of carbohydrates. Vitamin B_3 acts as a coenzyme in energy metabolism and fat synthesis. Vitamin B_6 is a group of 3 structurally similar compounds that all can be converted into the vitamin B_6 coenzyme which aids in the utilization of carbohydrates, fats, and proteins. Finally, vitamin B_{12} is involved in folate metabolism and in nerve function. Although energy drink container size is different among brands, on average, a typical can of 250 mL may contain 360% of the recommended daily allowance (RDA) of B_6, 120% of B_{12}, and 120% of B_3. In some of the more extreme energy drinks, such as 5-hour Energy, the addition of excess amounts of vitamins B goes up to 8333% of the RDA for vitamin B_{12} and 2000% of the RDA for vitamin B_6. B vitamins are found in a wide variety of foods, so that a standard diet is able to provide the full RDA. Moreover, since all of B vitamins are water-soluble, the excess vitamins are excreted from the body via renal excretion with the urines. Thus, although the consumption of large amounts of B vitamins is known to increase mental alertness and focus, once the RDA has been met, the excess quantity is eliminated. In any case, it should be underlined that the consumption of a large amount of B vitamins does not possess any adverse health effects [17].

12 Energy drinks and cardiovascular events

12.1 Brief summary of reported sudden cardiac arrest and ventricular arrhythmia cases

12.1.1 Case 1 (Rottlaender et al.) [57]

This is a case of congenital long QT complicated by torsades de pointes degenerating into ventricular fibrillation. A 22-

year-old woman experienced an out of hospital cardiac arrest "without prodromes in a discotheque." She was successfully resuscitated and admitted to the intensive care unit. Coronary angiography was normal as was left ventricular angiography. The search for alcohol and the use of illicit drugs was negative. The ECG recorded by the emergency medical services showed a prolonged corrected QT interval and genetic testing confirmed a long QT-1 syndrome. "Prior to cardiac arrest the patient consumed six cans of a caffeinated energy drinks within 4 hours" (type not disclosed). This corresponded to 480-mg caffeine within 4 h. An ICD was implanted associated with beta-blocker therapy. The follow-up visits at 6 months and 1 year were uneventful.

The authors did not suggest based on current literature any effect of energy drinks on the QT interval but postulated that high doses of caffeine may trigger life-threatening arrhythmias in patients with long QT.

12.1.2 Case 2 (Cannon ME et al.) [58]

A 25-year-old barmaid collapsed and was at first successfully resuscitated. On arrival at hospital, she was found in ventricular fibrillation but, despite resuscitative efforts, did not regain spontaneous hemodynamic activity. She was known to have mitral prolapse and occasional palpitations. The ECG prior to this event was normal. Her caffeine intake was limited voluntarily to one cup of tea a day but she was given a 55-mL bottle of "Race 2005 Energy blast" containing guarana and ginseng. She did not consume other caffeine substances. At autopsy, a "sclerosis and myxoid change of the mitral valve" was found. Toxicology screening was negative except for caffeine detected by gas chromatography-mass spectrometry at a concentration of 19 mg/L measured in the aortic blood.

We could not find the amount of caffeine in "Race 2005 Energy blast" which contains guarana and ginseng nor evaluate if the concentration of caffeine in the aorta was elevated and due to guarana or to additional caffeine or combination.

12.1.3 Case 3 (Berger AJ and Alford K) [59]

This 28-year-old amateur motocross rider experienced an out of hospital cardiac arrest. He was successfully resuscitated, and ventricular fibrillation was recorded. Sinus rhythm was restored after electrical shock. After his second race, he developed a mild retrosternal chest pain with no radiation, persistent, which subsided after 30-min rest. He "consumed 7–8 cans of caffeinated energy drinks between 8:am and his collapse, 7 hours later." (The brand of the energy drink is not specified). The only risk factor for coronary artery disease was smoking (6 pack-year history). The ECG recorded on admission was consistent with an evolving anteroseptal myocardial infarction. The laboratory tests showed elevation of troponin I and hypokalemia (3.0 mmol/L). The patient was given thrombolysis and commenced on intravenous heparin and loading doses of aspirin and clopidogrel. Coronary angiogram was normal, and the echocardiogram showed mild left ventricular enlargement and a hypokinetic anteroseptal segment.

This case illustrates the possibility of acute myocardial infarction probably related to coronary artery spasm, complicated by early cardiac arrest due to ventricular fibrillation following a heavy consumption of "caffeinated energy drinks" associated with heavy exercise [60].

12.1.4 Case 4 (Rutledge et al.) [61]

A 24-year-old man collapsed in a bar after consuming a "Red Bull®" energy drink containing 80 mg of caffeine and 1000 mg of taurine, which was combined with vodka. This occurred "after only a few sips" of the combination. Cardiopulmonary resuscitation was started by a bystander and Emergency Medical Services recorded ventricular fibrillation which was successfully defibrillated. The ECG in sinus rhythm showed "prolonged QRS duration." This patient has no known history of heart disease or of illicit drug, tobacco use, or family history of sudden death. This was the first time the patient consumed an energy drink. Laboratory tests revealed hypokalemia (K = 2.7 mmol/L) and decreased bicarbonate (CO_3H = 2 mg/dL). Blood alcohol level was low and drug screening in the urine was negative. The ECG showed changes consistent with the Brugada syndrome. An implantable cardioverter-defibrillator (ICD) was inserted.

The authors discussed the role of high doses of caffeine and taurine in triggering the ionic changes that may "expose" the Brugada syndrome and increase the risk of ventricular arrhythmias.

12.1.5 Case 5 (Avci et al.) [62]

"A 28-year-old man was admitted to the emergency department with ventricular tachycardia". Five hours before a basketball match, he drunk 3 cans of 250 mL of energy drink and complained of palpitations and nausea. Thirty minutes after the match, he lost consciousness and was in ventricular tachycardia. A 200-J shock restored sinus rhythm and the patient was admitted in the intensive care. The patient died on day 3 after a sudden cardiac arrest. The echocardiogram showed hypertrophy of the left ventricle "and antero-septal part of the heart." Until this event, the patient was apparently in good health and his past history and family history were unremarkable. He was consuming one energy drink per day containing 80 mg of caffeine for 7 months before the event.

This case of cardiac arrest and death was associated with acute and chronic ingestion of energy drink. It is not clear if the patient had associated hypertrophic cardiomyopathy. The

role of exercise combined with the acute and chronic consumption of energy drinks deserves special attention.

12.1.6 Case 6 (Goldfarb et al., case 1) [10]

A 19-year-old man presented with ventricular fibrillation after ingestion of a caffeinated energy drink (Monster®), a total of 160 mg associated with the use of marijuana and was successfully resuscitated. Clinical cardiac workup including transthoracic echocardiogram, cardiac catheterization, and electrophysiological study did not show any associated abnormality.

This description is based on fig. 1 of the authors as the case was not detailed in the text.

12.1.7 Case 7 (Goldfarb et al., case 2) [10]

A 57-year-old man experienced a cardiac arrest after he had consumed energy drinks containing a total amount of 1300 mg of caffeine. The workup showed left ventricular hypertrophy with regional left ventricular wall motion abnormalities. The patient was successfully resuscitated (aborted sudden death).

This description is based on fig. 1 of the authors as the case was not detailed in the text.

12.1.8 Case 8 (Ward et al.) [63]

A 45-year-old man underwent repair of tetralogy of Fallot at age 5 using a patch in the right ventricular outflow tract and who experienced several episodes of heart failure with an ejection fraction of 25%. An implantable cardioverter-defibrillator (ICD) was inserted. He consumed 3 Red Bull® energy drinks within 3–4 h and received an electrical shock from the device within 30 min after the third drink. Device interrogation showed non-sustained ventricular tachycardia and "several round of antitachycardia pacing at the onset of ventricular tachycardia then a 30J defibrillation shock for ventricular fibrillation."

The authors assume that without the ICD, the patient may have died which is likely. However, we cannot exclude the role of antitachycardia pacing in the possible induction of sustained ventricular tachycardia degenerating into ventricular fibrillation.

12.2 Other cardiovascular events (Table 4)

12.2.1 Case 9 (Terlizzi et al.) [64]

A 16-year-old volleyball player complained of orthostatic intolerance and transient loss of consciousness. She was diagnosed to have postural tachycardia syndrome. Searching for the cause, the authors discovered that she started 1 week before the onset of her symptoms to drink 4–5 cans a day of Red Bull®. Symptoms disappeared after she discontinued energy drink consumption.

This case describes a possible side effect of energy drinks as the discontinuation of the ingestion was associated with the disappearance of patient symptoms.

12.2.2 Case 10 (Nagajothi et al.) [65]

"A 23-year-old woman with no medical history" complained of palpitations and chest discomfort "after consuming GNC Speed shot" and a soft drink (Mountain Dew). Her heart rate was 219 beats/min. The ECG showed a supraventricular tachycardia resistant to carotid sinus massage which was terminated with 6 mg of IV adenosine.

In this case, the energy drink may have served as a trigger to a narrow QRS complex tachycardia which requires the presence of an accessory connection (AVRT) or dual AV nodal pathways (AVNRT).

12.2.3 Case 11 (Scott et al.) [66]

A 19-year-old man presented with a "dull chest pain radiating to his right arm associated with the feeling of being cold and shortness of breath." His past medical history was unremarkable except for a 2-year history of gastro-esophageal reflux. He had no risk factor for coronary artery disease and denied taking any illicit drug. In the week prior to admission, he has been drinking 2–3 cans of "Red Bull®" daily. The ECG on admission showed ST segment elevation in leads 1, II, aVL, and V4–V6 with ST depression in V1 and V2 consistent with the diagnosis of an acute postero-lateral myocardial infarction. Troponin I levels at 12 h were significantly elevated whereas the coronary angiography showed normal coronary arteries and mild left ventricular impairment. After 5 days of being pain-free, the patient was discharged from the hospital and the follow-up at 2 months was unremarkable. The patient was pain-free and abstinent from energy drinks.

The authors retained the diagnosis of acute myocardial infarction probably due to coronary spasm and suspected the role of excessive energy drink intake in the days preceding the event as a possible trigger.

12.2.4 Case 12 (Di Rocco et al.) [67]

A 14-year-old boy complained of a "fluttering sensation" 2 h after a running race. He "reported drinking an unknown quantity of a highly caffeinated drink the day before." He felt 5 days before admission "the same sensation" after drinking a Red Bull® energy drink. He had no medical history and an irregular heart rate around 130 beats/min and the ECG documented atrial fibrillation. The echocardiogram showed the absence of

structural heart disease. He converted to sinus rhythm after one dose of 7.5 μg/kg of digoxin.

The authors suggested since the patient had a normal ECG and "no endogenous" cardiac cause, that occurrence of atrial fibrillation after "consuming highly caffeinated drinks" may have induced the arrhythmia. Again, consumption of energy drinks associated with "vigorous athletic activity" is found in this report too. The amount of caffeine is not known.

12.2.5 Case 13 (Di Rocco et al.) [67]

A 16-year-old boy presented at the emergency department with "intoxication and vomiting" after a minor trauma. "He had ingested an unknown quantity of Red Bull® mixed with vodka at a party." He had a history of attention-deficit hyperactivity disorder, asthma, and allergies. At physical examination, he had an irregular heart rate at 160 beats/min and ECG confirmed atrial fibrillation with rapid ventricular response. He received 2 L of normal saline and was monitored. He spontaneously converted to sinus rhythm and remained hemodynamically stable.

This case of "atrial tachycardia/atrial fibrillation" occurred in a young boy without heart disease after consumption of energy drink combined with alcohol. As acknowledged by the authors, alcohol alone could have induced the arrhythmia. A prospective survey done in Denmark examined the association between the amount of caffeine consumed per day and the risk of development of atrial fibrillation or flutter and found no relation [68].

12.2.6 Case 14 (Kaoukis et al.) [69]

A case of "stress cardiomyopathy."

A 24-year-old man experienced after "small amounts of an energy drink" … "chest pain, acute respiratory failure and palpitations" … "associated with sinus tachycardia and occasional runs of supraventricular and ventricular tachycardias." The "echocardiogram at that time showed hypokinesis of all basal left ventricular segments with apical sparing and an ejection fraction of 35%." Chest x-ray revealed "bilateral fluffy pulmonary infiltrates." "Troponin was mildly increased, and serially measured brain natriuretic peptide was elevated at 8000 pg/mL." The patient was responsive to treatment. 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. Repeat examination 2 months after admission revealed complete normalization of left ventricular function, wall motion and wall thickness and the absence of any late gadolinium enhancement."

The authors consider this case as a reverse stress cardiomyopathy "triggered by consumption of an energy drink containing sympathomimetic substances".

12.2.7 Case 15 (Wilson et al.) [70]

A 17-year-old man presented to the Emergency Department with an acute chest pain irradiating to the left arm occurring at rest after "excessive consumption of caffeinated beverages prior to his symptoms" (Brand not specified). Of note, he had a history of "questionable myopericarditis diagnosed 1 year prior and thought to be secondary to a viral infection." The ECG showed marked ST segment elevation in leads II, III, and VF and in the precordial leads V3 toV6. The pain was relieved by intravenous morphine. CPK and troponin enzymes were elevated. The other abnormal laboratory tests include elevated white blood count, hypokalemia (K = 2.6 mEq/L), and low bicarbonate level (18 mEq/L). The patient has been drinking "a number of caffeinated energy drinks" (3–4 "Red bull®" with 80 mg of caffeine/can and 2–3 "Monster®" with 160 mg of caffeine/can) at around 8 p.m. the night prior to presentation. ECG changes improved after 3 h and the ECG normalized after 11 h. The patient was given nitroglycerin and aspirin 325 mg every 8 h because of suspected pericarditis. The echocardiogram showed a mild reduction in ejection fraction (50%) with apical hypokinesis but no sign of pericarditis. The patient denied taking any illicit drugs and the urine tests were normal except for opiates received in the ED.

The authors attributed the syndrome presented by the patient to coronary spasm possibly due to excessive ingestion of energy drinks. Diltiazem was administered and interrupted after 1 month as the patient was doing well.

12.2.8 Case 16 (Israelit SH) [71]

"A 24-year-old man presented to the Emergency Department with a one-hour history of crushing chest pain, nausea, and vomiting." He reported consuming about 20 cans of energy drink (XL) over the previous night but denied taking any drugs or drinking any alcohol. His medical history included overweight (BMI of about 40) and mild hypertension. "On arrival, he was anxious, sweating, and tachycardic (110 beats/minute), with blood pressure 90/60 mmHg. Heart sounds were normal on auscultation, and respiratory examination revealed slight basal rales, with no jugular vein distension." Electrocardiogram (ECG) on admission showed widespread ST segment elevation confirming acute myocardial infarction. "The ECG in their fig. 1 showed also sinus tachycardia, wide QRS complexes of the right bundle branch block type with left anterior hemiblock complicating an extensive anterior wall myocardial infarction (*our interpretation*)." He was given aspirin, oxygen, and morphine and was preceded to primary percutaneous intervention (PCI). While waiting for

the Cath-Lab team, the patient developed a wide complex tachycardia (*most likely ventricular tachycardia*) which was resistant "to DC shocks and a bolus of amiodarone," degenerating into ventricular fibrillation. The patient died despite resuscitative efforts. Analysis of the urines showed the presence of 3, 4-methylenedioxymethamphetamine (MDMA) also known as "ecstasy."

The authors' interpretation is that the large doses of caffeine contained in the energy drink cans ingested and the combination with MDMA were likely to have played a role in the death of this patient. This is apparently the first reported death following the ingestion of energy drinks.

12.2.9 Case 17 (Benjo et al.) [72]

A 24-year-old presented to the Emergency Department with a 10-h history of severe chest pain associated with nausea, multiple episodes of emesis, and palpitations which started 1 to 3 h after 3 drinks of vodka associated with an energy drink (brand not specified). He used marijuana in the week before but denied cocaine or any other drugs. "Two of his friends who shared the drinks had similar symptoms but no chest pain." On admission, the heart rate was 63 beats/min, and blood pressure was 138/94 mm Hg. ECG showed J point elevation in leads II, III, and VF and V2–V6. The echocardiogram showed apical hypokinesis. Coronary angiogram showed a "large thrombus of the left main coronary artery involving the origin of the circumflex (CX) and a second thrombus that occluded the distal left anterior descending coronary artery" (LAD). An intra-aortic balloon pump was placed, and coronary bypass grafting was done to the LAD with the left internal mammary and a saphenous bypass tract to the CX. The patient was discharged on warfarin.

This case of thrombus inside coronary arteries following consumption of energy drink associated with alcohol in a young man underlines the danger of this combination and a coagulation disorder. This patient required urgent coronary bypass surgery.

12.2.10 Case 18 (Dufendach et al.) [73]

A 13-year-old girl with long QT1 syndrome complained of "palpitations, chest pain, shakiness and dizziness to the emergency department because of continued chest after she consumed one can of an energy drink (160 mg of caffeine)." The ECG showed an "extreme QT prolongation" (QT/QTc of 494/624ms). She was put under ECG monitoring in the pediatric intensive care unit and over 24 h, she normalized the QT/QTc interval. She was given beta-blockers because she revealed that she had episodes of "faintness."

The interpretation of the authors is that in this patient with known congenital long QT syndrome, the energy drink has acted as "an epinephrine QT stress-test" explaining the excessive prolongation of the QT/QTc interval.

12.2.11 Case 19 (Polat et al.) [74]

A 13-year-old healthy boy was admitted for "a crushing midsternal chest pain and the ECG revealed 2–3 mm ST-segment elevation in leads II, III and VF and V3 to V5. The echocardiogram showed a left ventricular ejection fraction of 0.54 and moderate apical hypokinesis." Troponin I was increased. Coronary angiography showed an extensive dissection of the LAD coronary artery and a visible tear from the distal part of the vessel. This was managed conservatively. The description of the type and amount of energy drink is not provided. At the follow-up visit at 1 month, the patient was asymptomatic and the left ventricular function was normal.

This case of a coronary event associated with consumption of energy drink (brand and amount not specified) is puzzling with a coronary artery dissection of the LAD. The role of the energy drink is unclear.

12.2.12 Case 20 (Unal et al.) [75]

A 32-year-old man previously healthy "presented the emergency department with chest pain, palpitations and emesis which appeared 5-6 hour after drinking 5 bottles of energy drink" (brand not available). ECG showed marked elevation of ST segment from V2 to V6. Echocardiogram showed hypokinesis of the anterior, apical, and of the interventricular septum. Coronary angiogram demonstrated a thrombus obstructing 90% of the diameter of the left main coronary artery and a second thrombus obstructing 80% of the proximal LAD. Balloon angioplasty was performed achieving flow at the proximal segment of the LAD. After observation at the coronary care unit, the patient was discharged from the hospital on dual anti-platelet therapy.

This is another case of thrombus in the coronary artery requiring intervention in a young man. The role of a large amount of energy drinks within a relatively short period of time requires attention.

12.2.13 Case 21 (Solomin et al.) [76]

A 26-year-old man presented to the emergency department "for drinking his usual quantity (4 L of Monster®, Rockstar® and similar energy drinks)." He stated that he "drank … eight to ten 473 mL per day." ECG shows ST elevation consistent with an inferior wall myocardial infarction. He admitted to smoke one pack of cigarettes per day. He had no other predisposing factors to coronary artery disease except for moderate cholesterol and LDL elevation. The enzymes were not elevated. He underwent coronary

angiography which demonstrated a complete occlusion of the CX coronary artery and mild irregularities of the LAD. He had a stent placement and was discharged 2 days later.

This case of "acute thrombus occluding a coronary vessel" was attributed to coronary spasm induced by excessive consumption of caffeine contained in energy drinks with smoking being a possible trigger of vasospasm.

12.2.14 Case 22 (Satari et al.) [77]

A 28-year-old man who was healthy until the day he had acute onset of emesis becoming bloody at the end. He used to drink 2–3 beers and 2 Monster energy drinks per day for the past several months and chewing tobacco. He noted that the use of energy drink was associated with palpitations. His heart rate was irregular at 130 beats/min. The ECG showed atrial fibrillation and echocardiogram did not show any structural heart disease. He was treated with diltiazem and subsequently with metoprolol for control of heart rate. He converted spontaneously to sinus rhythm 48 h after admission. The follow-up at 6 and 12 months showed an absence of symptoms without any medication.

The authors acknowledge that this case of atrial fibrillation may have been caused by "possible sleep apnea in the setting of obesity and alcohol ingestion." However, they believe that energy drink ingestion played a role in inducing the arrhythmia.

12.3 Analysis of reported cases and comments

We found 22 cases of cardiovascular events associated with the use or abuse of energy drink consumption reported in the current literature. We have not included with due respect for the authors the case reports in which the role of energy drink consumption may have been purely coincidental or highly questionable [78, 79].

12.3.1 Cases of life-threatening arrhythmias

As shown in Table 3, 8 cases of life-threatening arrhythmias were reported including 5 cases of documented ventricular fibrillation, 2 of documented ventricular tachycardia, and the remaining case of ventricular tachycardia degenerating into ventricular fibrillation in a patient with an ICD. The age ranged from 19 to 57 years and 6 of these 8 patients were younger than 30 years. These case reports are heterogeneous. In 3 of these 8 patients, the energy drink brand was not specified, and the amount of caffeine could not be evaluated. In the remaining patients, the amount of caffeine ranged from "few sips" (case 4) to 1300 mg (case 7). In 3 patients, energy drinks were combined with alcohol (case 4) or the use of illicit drugs (2 patients). In 6 of the 8 patients, an underlying heart disease could have played a role. Of these, 2 patients (case 1 and case 4) had a hereditary potentially lethal syndrome, a long QT1 syndrome, and a Brugada syndrome possibly unmasked by the energy drink. In the 7 patients of cardiac arrests, 2 patients died (case 2 and case 5) and 5 were successfully resuscitated. Two patients (case 5 and case 7) were reported to have left ventricular hypertrophy which role in the event is not clear.

As aforementioned, caffeine is the main ingredient found in energy drinks. Cases of fatalities associated with caffeine intoxication have been reported. [80, 81] The mechanism by which caffeine may induce or trigger life-threatening arrhythmia is not known. However, experimental studies have shown that caffeine lowers the defibrillation threshold in both healthy dogs and dogs with myocardial infarction [82].

Although the reported cases of cardiovascular events are heterogeneous in many aspects, they are all associated with the use of energy drinks. The exact role of energy drinks in the genesis of life-threatening arrhythmias is difficult to ascertain particularly since a combination of factors in some cases may also have played a role in the event reported. In any case, the events are severe enough to raise a serious concern on the use or abuse of energy drinks.

12.3.2 Other cardiovascular events associated with energy drink consumption

Of the 14 case reports of Table 4, 7 patients had an ST segment elevation related to myocardial ischemia (2 patients) or infarction (5 patients). Except for 1 patient (case 21), 6 of the 7 patients had no history of coronary artery disease. The role of coronary artery spasm was suspected in 2 patients (case 11 and case 15). One child had a dissection of the LAD (case 19) and 2 patients a thrombus of the left main coronary artery (case 17) and of both the left main coronary artery and the proximal LAD (case 20). The remaining patient (case 16) died and the death was attributed by the authors to an acute anterior wall myocardial infarction probably related to excessive use of energy drinks.

Four reported patients had supraventricular tachycardias including 3 patients with atrial fibrillation (cases 12, 13, and 22) and one patient (case 10) a narrow QRS tachycardia. There was one case of "stress-induced cardiomyopathy" which resolved after discontinuation of energy drinks (case 14), one patient (case 18) had a long QT1 syndrome unmasked by energy drinks, and one patient (case 9) had orthostatic intolerance which resolved with energy drink discontinuation.

12.4 Selected aspects of energy drink consumption

12.4.1 Energy drinks and long QT syndrome

In a study of 24 patients with familial long QT syndrome, randomized double-blind cross-over study of energy drink,

Table 3 Life-threatening ventricular arrhythmias reported in association with energy drink consumption

Case no.	Ref.	Sex, age	Energy drink	Amount of caffeine	Other substance	Arrhythmia	Underlying disease	Outcome	Other follow-up
1	Rottlaender et al. [57]	F22	NA 6 cans	480 mg	None	Cardiac arrest due to TdP	Genetic testing Long QT1	Resuscitated ICD plus beta-blockers	1 year No recurrence
2	Cannon et al. [58]	F25	Race 2005 Energy blast	NA	None	Ventricular fibrillation	Mitral valve prolapse	Died	Autopsy caffeine level in aorta
3	Berger and Alfort [59]	M28	NA 7–8 cans	NA	NA	Cardiac arrest Ventricular fibrillation	None Normal coronary angiogram	Developed acute MI 7 h after ingestion	Coronary spasm?
4	Rutledge et al. [61]	M24	Red Bull	80 mg (?)	Vodka	Ventricular fibrillation	Brugada Syndrome	ICD implanted	Aborted sudden death
5	Avci et al. [62]	M28	3 cans 80-mg caffeine	240 mg	None	Syncope after exercise VT	LVH	Cardiac arrest Death on day 3	
6	Goldfarb et al. [10]	M57	NOS	1300 mg	"Ecstasy"	Cardiac arrest	LVH	NA	Aborted sudden death
7	Goldfarb et al. [10]	M19	Monster	160 mg	Marijuana	Ventricular fibrillation	None	NA	Aborted sudden death
8	Ward et al. [63]	M45	Red Bull 3 cans Within 3–4 h	249 mg	NA	Severe dizziness AICD shock within 30 min of ingestion	Repair of tetralogy of Fallot Patch in the RVOT AICD age of 40 HF EF, 25%	Non-sustained VT Antitachycardia pacing Defibrillator shock for ventricular fibrillation	NA

Table 4 Other cardiac events associated with energy drink consumption

Case no/ Authors	Sex, age	Brand of energy drink	Caffeine content	Combined substance	Symptoms	Cardiac event	Underlying disease	Other and outcome
9 Terlizzi et al. [64]	F16	Red Bull® 4–5 cans	320 mg to 400 mg/day	NA	Orthostatic intolerance and transient loss of consciousness	Postural tachycardia syndrome	None Volleyball player	Symptoms disappeared and tests normalized after ED discontinuation
10 Nagajothi et al. [65]	F23	GNC Speed Shot	760 mg (?)	Mountain Dew soda	Palpitations and chest discomfort HR regular 219 beats/min	Supraventricular tachycardias resistant to carotid sinus massage	None	Terminated with 6 mg of IV adenosine
11 Scott et al. [66]	M19	Red Bull® 2–3 cans/day	160-240 mg the week before	None	Chest pain ST elevation	Acute extensive myocardial infarction	None Coronary spasm?	Doing well 2 months later
12 Di Rocco et al. [67]	M14	NA Highly caffeinated drink the day before and 1 can of Red Bull a week before	NA	NA	"Fluttering sensation"	Atrial fibrillation	None (echo)	Converted to sinus rhythm after one dose (7.5 μg/kg) of digoxin Asymptomatic at 1-month visit
13 Di Rocco et al. [67]	M16	Red Bull®	NA Unknown quantity	Vodka Medications Amphetamine and dextroamphet-amine 30-mg loratadine, montelukast	Intoxication and vomiting after "minor trauma"	Atrial fibrillation Rate, 160 beats/min	No structural heart disease Attention-deficit, asthma, allergies	Received 2 L of normal saline Spontaneous conversion 12 h later Asymptomatic 1 week later
14 Kaoukis et al. [69]	M24	NA	NA "small amounts"	None	Chest pain heart failure	Stress cardiomyopathy	None	Normalization after 2 months
15 Wilson et al. [70]	M17	Red Bull® Monster® Night before	180–320 mg 320–480 mg	None	Acute chest pain	ST elevation Coronary spasm	History of Myopericarditis	Diltiazem interrupted after 1 month Patient doing well
16 Israelit et al. [71]	M24	XL® 80 mg/can	1600 mg the night before	"Ecstasy"	Crushing chest pain	Diffuse ST elevation Anterior wall myocardial infarction	Mild hypertension	Wide QRS tachycardia Ventricular fibrillation Died
17 Benjo et al. [72]	M24	Energy drink (?)	NA	Vodka Marijuana	Severe chest pain	T wave changes and J point elevation	None	Thrombosis of the left main coronary artery
18 Dufendach [73].	F13	NA Caffeinated 160 mg Energy drink	160 mg	None	Palpitations Chest pain Dizziness	Sinus tachycardia Extreme QT prolongation Monitored	None LQT1 unmasked by energy drink	QT/QTc normalized within 24 h Discharged after 2 days
19	M13	NA	NA	None	"Crushing" chest pain	ST elevation Myocardial infarction	None	Spontaneous

Table 4 (continued)

Case no/ Authors	Sex, age	Brand of energy drink	Caffeine content	Combined substance	Symptoms	Cardiac event	Underlying disease	Other and outcome
Polat et al. [74]								coronary dissection of the LAD coronary artery
20 Unal et al. [75]	M32	NA 5 bottles of energy drinks (?)	NA	None	Chest pain Palpitations Emesis	ST elevation Acute anterior wall myocardial infarction	None	90% thrombosis main left coronary artery and 80% proximal LAD
21 Solomin et al. [76]	M 2-6	Monster® Rockstar® and other 8–10,473 mL drinks/day	NA But probably exceeding 640 mg	None	Chest pain radiating to the left arm and jaw 9 h before visit to ER	ST segment elevation in II, III and VF Acute inferior wall MI	Coronary artery disease	Significant occlusion of the circumflex Angioplasty and stent
22 Sattari et al. [77]	M28	Monster®	320 mg	Beer 2–3	Acute bloody emesis Palpitations for several months	Atrial fibrillation 130 beats/min	None	PPI Diltiazem then metoprolol for AF Spontaneous conversion

the participants acted as their own control. [83] They were randomized to drink either one can of Red Bull® at time 0 and a second can 30 min later or 2 cans of a control drink. There was no significant change in QTc (12.5%). However, 3 patients had a QTc prolongation above 50 ms after energy drink consumption. Systolic and diastolic blood pressure significantly increased following energy drink [83]. As appropriately stated by Schwartz and Dagradi, [84] the total dose of caffeine (160 mg) is low but this study should not underestimate the risk of ventricular arrhythmias triggered by energy drinks in the vulnerable population of patients with congenital long QT. Shah et al. [85] showed that QTc prolongation occurred in a healthy volunteer after two 16-oz of Monster® energy drink (320 mg of caffeine over a 45-min period).

12.4.2 Energy drink consumption, platelet aggregation, and endothelial function

Energy drink may be associated with myocardial ischemia or infarction. Worthley et al. [86] studied in 50 healthy volunteers the platelet aggregation and endothelial function before and 1 h after 250 mL (1 can) of energy drink. They found that energy drink acutely increased platelet aggregation and reduced endothelial function in healthy volunteers.

12.4.3 Energy drinks mixed with alcohol and illicit drugs

Energy drinks are often consumed alone but they are also frequently mixed with alcoholic drinks particularly in underage and young drinkers as emphasized by several authors [87–89]. Energy drinks can elevate the level of alcohol consumption, decrease the perception of intoxication, and induce impaired driving, risky sexual behavior, and alcohol dependence [88]. It has been found that those who are regular consumers of energy drinks have a tendency to use more often illicit drugs. However, a recent survey performed in the UK seems to indicate that the occasions in which the users of energy drinks mix them with heavy alcohol are not more common than those of alcohol only [90].

12.4.4 Energy drinks and exercise

As aforementioned, caffeine was found to impair myocardial blood flow even in healthy individuals during exercise [34]. A meta-analysis showed that energy drinks improved physical performance in muscle strength and endurance and sport-specific actions and the meta-regression showed a significant association between performance and taurine dosage but not with caffeine dosage. In any case, athletes and young adolescents may be tempted to improve their performance by using energy drinks [91, 92]. However, 2 of the 8 reported cases of

ventricular tachycardia or ventricular fibrillation associated with consumption of energy drinks occurred during or after vigorous physical activity.

12.4.5 Energy drink consumption during pregnancy

Caffeine intake included in soft and energy drinks was associated in pregnant women with decreased birth weight and increased odds of baby being small for gestational age, according to a study conducted by the Norwegian Institute of Public Health [93]. This study was based on 108,000 pregnancies and the data of repeated ultrasound offered to all pregnant women in Norway.

13 Conclusion

Our systematic and critical review of the literature confirms updates and extends the concern that should be derived from the literature based mainly on reported cases [2, 9–14]. There are only a limited number of studies related to energy drinks [13]. In some reported cardiovascular events, the relation cause to effect was probable as the events resolved after discontinuation of energy drink consumption. In others, the role of energy drink in triggering the cardiovascular event could only be suspected but not ascertained. In most cases, the event was attributed to the high amount of caffeine and/or because no other known cause could be questioned. The mechanism of these cardiovascular complications is still unclear although it is known that high doses of caffeine may be associated with life-threatening arrhythmias or, at very high doses, death [80, 81]. We agree with other authors [3] that well-designed prospective studies are needed to clarify the role of energy drinks in reported cardiovascular events. Nevertheless, these cardiovascular events are worrisome enough to raise a serious concern and to issue recommendations for better prevention.

14 Recommendations

The European Cardiac Arrhythmia Society would like as other Societies or Regulatory authorities [94–96] to draw attention on the possible danger of energy drinks use or abuse. As caffeine is the main component of this beverage, the population should be aware of its content in each brand and on the cardiovascular risk associated with the excess use of these beverages. It should be stressed that the reports analyzed have not the value of scientific studies and indicate but not demonstrate that overconsumption or misuse of energy drinks may be associated with cardiovascular events. More properly designed studies are needed to verify the current hypothesis on the role played by energy drinks in the cardiovascular events reported.

The recommendations should be addressed first to physicians particularly those who are dealing with the young population such as pediatricians and emergency doctors. They should be aware of the side effects of these beverages, the signs of toxicity, and complications particularly life-threatening cardiovascular events that have been reported in apparently healthy young individuals following the occasional or/and regular consumption of these beverages. The parents of adolescents and educators should be also informed of the arrhythmogenic effects of the abuse of energy drinks [5].

In order to prevent adverse effects associated with energy drink consumption, these beverages should not be recommended in:

- Children younger than 14 years old or children with known underlying heart disease [97]

"Children and adolescents should only consider use of energy drinks and energy shots after consideration of the amount of carbohydrates, caffeine and other nutrients contained in energy drinks and energy shots and a thorough understanding of the potential side-effects." [94]

- A cardiological workup including an electrocardiogram may be desirable to detect patients with long QT syndrome or Brugada syndrome which represents a population at higher risk of sudden cardiac death and an echocardiogram indicated when underlying structural disease is suspected.
- The total content of caffeine for a young adult should be less than 400 mg/day although if taken in a short period of time, such amount may put susceptible patients at risk of cardiovascular adverse events.
- In children over 14, the total daily amount of caffeine should be less than 2.5 mg/kg body weight.
- Energy drinks should not be mixed with alcohol or illicit drugs (marijuana, ecstasy)
- Energy drinks should not be used before or during sports practice or heavy exercise.

It is the role of the Regulatory authorities to issue proper legislations and recommendations to the general population particularly adolescents and young adults, to their parents or educators and to alert them on the possible complications related to excessive use of energy drinks. There is no specific legislation at the European level for energy drinks. However, the European Food Information to Consumers Regulation (EU N° 1169/2011) labelling of energy drinks includes "High caffeine content. Not recommended for children or pregnant or breast-feeding women" followed by the *indication of the amount of caffeine per 100 mL in brackets.*

Some EU member states have specific regulatory provisions on energy drinks. For example, in Belgium, the

"Conseil Supérieur de la Santé" recommended (December 2, 2009):

- Not to consume regularly energy drinks and to limit the total amount of caffeine per day to less than 400 mg and even less than 300 mg
- Not to combine the use of energy drinks with alcohol or heavy exercise
- Not to authorize the use of energy drinks during pregnancy (as it affects the development of the fetus) or in breastfeeding women.
- In children before the age of 16 years and to the caffeine sensitive persons.

We can only support such recommendations which should be included in the labelling of these beverages. Only controlled studies will allow to characterize the risk related to substances other than caffeine in particular taurine and D-glucuronolactone. Until we obtain such information, the above recommendations should be observed for consumer protection.

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