

## ASSOCIATION BETWEEN ENERGY DRINKS AND CARDIOVASCULAR EVENTS: A LITERATURE REVIEW

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### Contribution

SZ conceived the idea. Data collection and manuscript writing was done by SZ, RSR, HMM, SA, UM, and HMSJ. All the authors contributed equally to the submitted manuscript.

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### ABSTRACT

There has been a tremendous increase in the consumption of high-energy (ED) drinks in the last decade. This has been equally popular among teenagers and adults of both genders and is marketed to boost energy, alertness, and performance and prevention of fatigue. Although ED contains a variety of ingredients such as taurine, guarana, L-carnitine and multivitamins, it is the caffeine that plays a significant role in affecting different systems such as cardiovascular (arrhythmias), neurological (seizures) and neuropsychiatric system (agitation and suicidal ideation). Symptoms of caffeine intoxication include palpitation, rise in blood pressure, insomnia, seizures, tremors and irritability, gastrointestinal symptoms, disturbance of sleep cycle and in rare cases death. However, in this review, we focused mainly on cardiovascular symptoms in addition to contents, mode of action and pharmacokinetics of ED. As several studies point towards mortality due to arrhythmias after drinking ED, it is important to concentrate on these deleterious effects.

**Keywords:** Energy Drinks, Caffeine, Cardiovascular Events

## INTRODUCTION

High-energy drinks (ED) are becoming popular among adolescents and athletes. They contain a high content of taurine, guarana, caffeine which all are marked as active ingredients that increase attentiveness, cognition, physical and emotional execution.<sup>1-4</sup> Since 'Red-bull' development in 1997, several brands have been made and marketed, with the 'Red-bull' having the largest share in the market.<sup>5</sup> In 2010, almost 9 billion drinks were consumed by US residents, and the sale of energy drinks skyrocketed to \$3.4 billion in 2019 from \$2.8 billion in 2015.<sup>6</sup> However, perception about the consumption of ED started to change after several reports of sudden unexplained deaths in different countries among healthy young-adults, which were possibly due to arrhythmias, and also several cases of emergency visit pertaining to acute intake of EDs.<sup>1,7,8</sup>

It was found that EDs cause several adverse metabolic effects predominantly affecting cardiovascular system (arrhythmia) and neurological system (seizures, agitation and suicidal ideation).<sup>9</sup> These drinks are often taken with other stimulants such as alcohol, nicotine which augment the effects tremendously and further deteriorate the condition.<sup>10-12</sup> However, there are many case reports, observational and interventional studies that have highlighted the effect of EDs on CVS particularly changes in blood pressure and prolongation of QTc interval. We will discuss potential changes in cardiovascular system which are associated with intake of EDs along with their composition and pharmacokinetics.

## Composition of Energy drinks

Energy drinks contain several additives but the most important one is caffeine, which is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, yerba mate and many other plants.<sup>13</sup> Other than caffeine, there are many other components e.g. sugar, taurine, guarana, glucuronolactone, herbal extract such as ginseng and ginkgo bioba, vitamins e.g. vitamin B12.<sup>14,15</sup> Although FDA limits 0.2 mg of caffeine per mL, an average ED contains 0.34 mg of caffeine per mL.<sup>1,16,17</sup> Each brand has its own

combination of ingredients in different quantities, and some do not disclose the quantity of caffeine.<sup>18,19</sup>

## Pharmacokinetic and mechanism of action EDs

After ingestion, caffeine is readily absorbed from the intestinal tract and converted in the liver to Paraxenthrine by cytochrome p450 monooxygenase contributing almost more than 90% of its clearance.<sup>20-23</sup> So, its metabolism is affected by other drugs such as alcohol, nicotine and other inducers and inhibitors of cytochrome p450. Plasma half-life of caffeine is 2 to 8 hours, which could be reduced by smoking, but it increases to 18 hours in pregnancy.<sup>24-26</sup> As Caffeine is hydrophobic, it can cross any barrier such as blood-brain, placental and testicular barrier.

Caffeine is a stimulant and plays its role by competitively antagonizing the adenosine receptor rising dopamine and glutamate concentration, which in turn inducing cortical and neuronal activity.<sup>27-30</sup> Similarly, it also raises myocardium cAMP, which exerts a positive inotropic effect on the heart by competitively inhibiting phosphodiesterases. Furthermore, it also increases sympathetic activity by raising plasma level of epinephrine and norepinephrine.<sup>29,31</sup> At a low level, caffeine causes an increase in heart rate, hypertension, gastrointestinal symptoms and stimulation of neurological system.<sup>13,32</sup> However, during acute toxicity, it has a detrimental effect on the heart such as tachycardia that can lead to tachyarrhythmia. The basic mechanism is the rapid efflux of calcium from sarcoplasmic reticulum which in turn elevates epinephrine, thereby causing coronary artery vasospasm, supra-ventricular and ventricular arrhythmias.<sup>33-36</sup> While other components of ED also play their role indirectly by increasing weight and disturbing lipid profile, caffeine directly has a role in upsetting heart.<sup>37</sup> It has also been reported that taurine has an additive effect on caffeine action by enhancing its physiologic role.<sup>38-39</sup> As one study reported tachycardia and hypertension after acute ingestion of EDs, other reported an increase in cardiac output.<sup>40,41</sup> Another study demonstrated elevation of heart rate by taking account of electrocardiography, and reported an increase in

stroke volume and compared it between exercise and control group.<sup>42</sup>

There has been a significant rise in both systolic and diastolic blood pressure observed among people consuming EDs, and this is due to caffeine effect on peripheral vascular resistance by inhibiting adenosine receptors and releasing dopamine.<sup>38,43</sup> To summarize, EDs play an important role in CVS by changing the myocardial activity, stroke volume, heart rate, blood pressure and rhythm.

## **RISK OF CARDIOVASCULAR EVENT**

### **Effect on Heart rate (HR) and Blood pressure (BP)**

Several studies investigated the effect of EDs on BP, but they have different results which may be due to several factors such as duration, intensity, volume-consumed and frequency of exposure.<sup>41,44</sup> Ragsdale et al. reported no change in the BP irrespective of rest or during exercise.<sup>45</sup> However, Grasser et al. noted a significant increase in both systolic and diastolic BP, by almost 5 and 6 mmHg respectively, as well as increases in heart rate. This study included 25 healthy young-adults who consumed 'Red-bull' and tap water, and their cardiovascular measurement was recorded before and 2 hours after consumption<sup>41</sup>. Similarly, Frank et al. demonstrated the combined effect of caffeine and taurine on BP and showed both contents raised Blood pressure significantly than when consumed individually.<sup>5</sup> However, Hypertensive patients showed a marked rise in blood pressure so they have to avoid EDs.<sup>14</sup> Likewise, there are evidences that report hypertension after chronic use of EDs.<sup>14</sup> Moreover, Elitoke et al.<sup>44</sup> and Steinke et al.<sup>40</sup> reported an almost 3-7 beat/min increase in HR after 2-hour post-ingestion EDs and similar results were shown by Grasser et al.<sup>41</sup> To summarize, there has been a notable increase in Blood pressure and Heart rate observed in many studies so that an average increase of systolic, diastolic blood pressure and heart rate is 6-10mmHg, 3-6mmHg and 3-7 beat/min accordingly.

### **Effect on Corrected QT (QTc) Interval**

Several studies demonstrated that the most significant effect of EDs is on changing the conductance of the heart. In numerous studies, the predominant increase in QTc interval has been

reported in both healthy and genetically susceptible individuals in association with consumption of EDs. Caffeine could cause arrhythmias by disturbing cardiac ion channels in combination with other contents.<sup>47</sup> Fletcher et al.<sup>48</sup> demonstrated that prolongation of QTc interval is not only caffeine mediated and other ingredients also play their role, as well as raising catecholamine concentration in the body. A Sachin et al.<sup>49</sup> a randomized control study, included 44 healthy volunteers and demonstrated acute effects of EDs on electrocardiogram and BP, and, interestingly, there was a significant increase in QTc interval and blood pressure. Similarly, a case report of a 13-year old girl having type 1 LQTS presented to the emergency department after ingestion of 16-oz can of an ED with symptoms of palpitations, chest pain, shakiness, and dizziness. An electrocardiogram was taken and depicted a QTc of 561 ms, with a follow-up electrocardiogram done 1 h later revealing a QTc of 557 ms at 96 bpm for confirmation.<sup>50</sup> Therefore, sudden cardiac arrest can be the outcome of sequelae of prolonged QT which can lead to torsades de points and ventricular arrhythmias, and, hence, reported in a case of a 22-year old female who had consumed six cans of an ED and undergone cardiac arrest. Series of tests revealed that she was suffering from type 1 long QT syndrome and EDs consumption precipitated arrest.<sup>51</sup> To sum up, there is an increase in QTc interval in acute consumption of EDs.

## **RISK OF SUPRAVENTRICULAR AND VENTRICULAR ARRHYTHMIAS**

Caffeine present in high-energy drinks is considered to be arrhythmogenic.<sup>52</sup> Numerous studies are demonstrating the association between EDs and arrhythmias, both supraventricular and ventricular. Caffeine consumption can precipitate or exacerbate supraventricular arrhythmias.<sup>52</sup> Caffeine in EDs is shown to increase the epinephrine and norepinephrine level in the body and disturbing the conductance of heart by changing cardiac ions, all of which may precipitate ventricular tachycardia and fibrillation.<sup>18,29,31</sup> Turagam et al. reported atrial fibrillation among the young adults after acute ingestion of EDs although it is extremely rare for young population to have atrial fibrillation unless they have congenital heart disease.<sup>53</sup> A case report of a 13-year old Spanish boy who had atrial fibrillation during football match after consuming ED.<sup>54</sup> In contrast, as a large study in America showed a protective effect of coffee drinking on the rhythm of heart<sup>55</sup>, a study reported that being antioxidant, caffeine protects against atrial

fibrillation.<sup>56</sup> Whereas in another study reported that the combined effect of caffeine and other components in EDs causes precipitation of atrial fibrillation.<sup>57</sup> The role of caffeine in causing arrhythmias still remains debatable because there are contradicting studies regarding role of EDs in arrhythmias in which one study shows no causation,<sup>58-59</sup> while other depicts a relationship between the two.<sup>1,60</sup> Mattioli et al. also demonstrated that three young individuals went on developing atrial fibrillation after acute intake of a large amount of ED.<sup>61</sup> Similarly, a case of a 58-year old previously-healthy person presented with shortness of breath and palpitation after prolonged consumption of ED for 6 months. ECG showed atrial fibrillation and Echocardiography depicted ejection fraction reduced to 45% with an increase in the size of heart.<sup>62</sup> Ward et al. reported ventricular fibrillation in a patient having congenital heart disease after consuming three 'Red-bull' energy drinks.<sup>63</sup> Likewise, a case report of 19-year old boy developed ventricular fibrillation and eventually cardiac arrest after consuming 'Monster ED' and marijuana.<sup>18</sup> Another case of ventricular fibrillation has been reported in a young adult after ingestion ED along with alcohol.<sup>64</sup>

## Risk of Myocardial Ischemia or Infarction

Because of an increase in the intracellular level of calcium, effluxed from sarcoplasmic reticulum,<sup>34,36</sup> intake of caffeine may cause coronary artery vasospasm, which leads to ST-segment elevation in ECG. A case report depicting a young boy presented to emergency with the crushing chest pain radiating to the left arm, ECG changes are consistent with ST-segment elevation MI, and his cardiac enzymes were elevated also. He had a notable history of ED drinking for a week. Cardiac angiography showed normal coronary arteries, and, hence, a diagnosis of coronary artery vasospasm was made.<sup>36</sup> Rutledge et al. described a young Caucasian male with mild hypertension who came to emergency with symptoms of chest pain, nausea and vomiting after acute intake of 20 cans of ED.<sup>64</sup> Upon admission, ECG revealed diffuse ST-segment elevation which confirmed the diagnosis of myocardial infarction. However, he died because of ventricular fibrillation while waiting for PCI. Similarly, Solomin et al. demonstrated the development of myocardial infarction in 24-year old Hispanic male after excessive consumption of ED although he also used to smoke regularly.<sup>65</sup> Coronary angiography confirmed the blockage of left circumflex artery so drug-eluting stent was placed to reverse changes in

ECG. Caffeine can also disrupt platelet aggregation and microvascular endothelial function, thereby further contributing towards myocardial infarction and ischemia.<sup>66</sup>

## Risk of aortic dissection

An increase in blood pressure, heart rate and sympathetic activity in association with consumption of ED can lead to aortic dissection especially among individuals with pre-existing medical conditions.<sup>14,67</sup> Jonjev et al. reported a healthy man with no previously known co-morbidity, presented to emergency with sudden onset of chest pain although he reported having two ED before developing symptoms.<sup>68</sup> Upon presentation, echocardiography was done and showed De Bakey type 1 aortic dissection. Surgery was performed and the patient was discharged without any complication. The same case report showed a 26-year old Caucasian male having a bicuspid aortic valve along with dilation of aorta presented in emergency after consuming few EDs with symptoms of sudden chest pain. Further imaging techniques revealed aortic dissection. Same study reported another case with same result. Individuals with the condition like Marfan syndrome or bicuspid aortic valves are more prone to develop aortic dissection upon consuming EDs.<sup>69</sup> In all of the above mentioned cases, interestingly, aortic dissection occurred after the ingestion of a large amount of EDs which could be due to rising blood pressure and catecholamine surge, hence, elevating the stress on the aortic walls.

## Risk of cardiomyopathy

As caffeine in the EDs is associated with antagonizing the adenosine receptors, releasing catecholamine and increasing intracellular calcium, all of these actions induce certain stress on myocardium.<sup>15,39</sup> There is only a single case of cardiomyopathy, demonstrating a 24-year old man presented to emergency with chest pain, palpitation and respiratory failure after acute consumption of a large amount of ED.<sup>70</sup> Electrocardiogram revealed nonspecific T-wave inversion in leads I and aVL, and it also showed sinus tachycardia along with frequent runs of ventricular tachycardia. Echocardiogram showed a decrease in ejection fraction. Cardiac MRI was performed which revealed globally increased myocardial wall thickness. Considering all of the above findings, the diagnosis of Takotsubo Cardiomyopathy was made. The patient was

followed up for the next few months and all of the findings became normal.

In Summary, Cardiovascular events occur due to acute and chronic exposure of EDs. Although some of the complications caused by use of ED are debatable and their mechanism of action is unknown, genetic susceptibility could make some people more prone to have complications than others. A summarized description of cardiovascular events caused by EDs is shown below in the table. (Table 1).

**Table 1: Summary of Cardiovascular Events reported after the use of Energy Drinks**

Cardiovascular Events	Author Name	Year of Publication
Elevated Blood Pressure and Increased Heart Rate	Grasser <i>et al.</i>	2014
	Franks <i>et al.</i>	2012
	Steinke <i>et al.</i>	2009
Hypertension	Usman <i>et al.</i>	2012
QT Interval Prolongation	Sachin <i>et al.</i>	2019
	Fletcher <i>et al.</i>	2017
Atrial Fibrillation	Turagam <i>et al.</i>	2015
	Izquierdo <i>et al.</i>	2016
	Mattioli <i>et al.</i>	2016
	Peake <i>et al.</i>	2007
Ventricular Fibrillation	Ward <i>et al.</i>	2014
	Rutledge <i>et al.</i>	2012
	Goldfarb <i>et al.</i>	2014
Myocardial Infarction	Scott <i>et al.</i>	2015
	Rutledge <i>et al.</i>	2012
	Solomin <i>et al.</i>	2015
Aortic dissection	Silverio <i>et al.</i>	2015
	Jonjev <i>et al.</i>	2013
	Humphery <i>et al.</i>	2015
Takotsubo Cardiomyopathy	Kaoukis <i>et al.</i>	2012

## CONCLUSION

All of the previously mentioned studies demonstrates a strong association between EDs consumption and cardiovascular complications. Several case reports, observational studies and meta-analysis have been done regarding the acute ingestion of EDs and their effect on myocardial

activity. Acute intoxication of EDs can be severe enough to cause hypertension, QTc prolongation, atrial and ventricular arrhythmias, myocardial infarction, coronary vasospasm, aortic dissection, cardiomyopathy and cardiac arrest. These conditions are exacerbated in case of any genetic condition such as type 1 LQT and in case of substance abuse or structural anomaly. According to studies, EDs can be detrimental when taken alone or in combination with any other stimulant. However, there is dearth of research concerning the chronic effect of EDs on heart. As only caffeine is considered to be well studied among all the contents in the EDs, other ingredients still require a lot of work so that their action can be understood. To sum up, although many studies have been done to associate EDs with cardiovascular events, there is still lack of information for providing sufficient evidence, thereby suggesting well-designed studies to fill in the gap.

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