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REVIEW

Effects of energy drinks on the cardiovascular system

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Abstract

Throughout the last decade, the use of energy drinks has been increasingly looked upon with caution as potentially dangerous due to their perceived strong concentration of caffeine aside from other substances such as taurine, guarana, and L-carnitine that are largely unknown to the general public. In addition, a large number of energy drink intoxications have been reported all over the world including cases of seizures and arrhythmias. In this paper, we focus on the effect of energy drinks on the cardiovascular system and whether the current ongoing call for the products' sales and regulation of their contents should continue.

Key words: Energy drinks; Caffeine; Taurine; Guarana; Cardiovascular effects

Core tip: The last decade has witnessed a great surge in the consumption of energy drinks which coincided with an increased rate of reported cases of intoxications resulting in cardiovascular adverse effects especially arrhythmias, although most of such cases were associated with alcohol, stimulants, or rapid consumption in a short period of time. In our paper, we summarized the research pertaining to the most common components of the energy drinks in an attempt to evaluate whether the call for control of the products is merited, some of which had surprising possible health benefits.

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INTRODUCTION

The last decade has witnessed the greatest rise in the consumption of non-steroidal energy supplements for the specific purpose of boosting athletic performance and concentration. For many years, the use of energy drinks (ED) has been perceived as potentially dangerous due to their strong concentration of caffeine and presence of other substances such as taurine, guarana, and L-carnitine amongst others. In France, the use of Red Bull™ was banned at one point until the rule was reversed by the European Union on claims of the lack of evidence for its toxicity. The controversy surrounding energy drinks heightened recently due to the increasing reports of energy drink toxicities, most alarmingly in regard to heart rhythm and central nervous system abnormalities such as atrial fibrillation and seizures, respectively. We aim to focus on the effect of energy drinks on the cardiovascular system and whether the call for the products' sales and regulation of their contents has merit.

SCOPE OF THE ISSUE

In recent years, the market for energy drinks has thrived and after 50 years in the market, the consumption of these beverages has increased exponentially[1]. Along with a growing global market, emergency room visits due to the consumption of energy drinks have increased as well. The Substance Abuse and Mental Health Services Administration revealed that 20783 people visited the emergency department with complaints involving caffeine rich energy drinks in 2011. Over the period from 2007-2011, ED-related emergency department visits in the United States doubled[2]. Due to their high consumption, lack of evidence, and occasional acute adverse health effects, the safety of energy drinks has been called into question. Our review will specifically focus on the cardiovascular effects of the ingredients contained in EDs.

As promisors of prolonged arousal, boosted athletic performance, and increased concentration, energy drinks have become popular supplements in the past few years. A recent study of 1620 nursing students noted 78.1% reported ED use. The students consumed an average of 1.6 cans per week, ranging from 1 to 30 cans per week[3]. Certain ED company claims have been found to be true. One placebo controlled study found that certain important aspects of cognitive function can be improved by a single energy shot. The study was performed on partially sleep-deprived healthy individuals and the effect was noted to last for up to 6 h[4]. Another study found that subjective ratings of vigor and fatigue were improved after the consumption of energy drinks, although, objective performance did not improve and, in fact, seemed to worsen over time[5].

With increased stress to perform academically, athletically, and socially, it is not surprising that most consumers of EDs are teenagers and young male adults[6,7]. It should be noted that ED consumption cannot be looked at as a separate entity as co-ingestion with alcohol, drugs, and other pharmaceuticals has become a widespread practice. A cross-sectional survey conducted in 2012 reported that 85 emergency department patients, that were there for ED related events, showed that illicit stimulants such as cocaine and methamphetamine were often co-ingested[8]. Another study found that males were more likely to co-ingest alcohol or drugs, whereas in females, co-ingestion of other medications was more common[9]. It should be noted that the half-life of caffeine was found to increase by up to 72% with its coingestion with alcohol, thereby enhancing the effects of EDs[10].

PURPORTED EFFECTS OF ENERGY DRINKS AND THEIR CAFFEINE-RELATED CAUSAL ROLES ON THE CARDIOVASCULAR SYSTEM (FIGURE 1)

Physiologic effects on vital signs

Evidence of reported energy drinks-related cardiovascular adverse effects has helped to further raise suspicion of these beverages. It is widely believed that caffeine, particularly at high doses, is associated with multiple cardiac comorbidities including palpitations and a number of arrhythmias such as atrial fibrillation and supraventricular and ventricular ectopy. Caffeine's effect in acutely raising the blood pressure is also thought to stress the cardiovascular system, furthering the likelihood of it causing arrhythmia. Such an elevation in blood pressure has been also shown to be more prominent in the elderly and those with underlying hypertension. A study of 20 young healthy humans explored the effects of Red Bull along with induced mental stress. It was found that compared with the ingestion of water, ingestion of a 355 mL can of Red Bull imposes a cumulative cardiovascular load, increasing systolic BP by about 10 mmHg, diastolic BP by about 7 mmHg, and heart rate by 20 beats/min, and decreasing cerebral blood flow velocity by -7 cm/s[11].

Several studies have found energy drinks have been shown to induce hypertension compared to placebo. A recent study asked fifteen recreational runners to complete five exercise trials. The subjects ingested one of three energy drinks or a placebo one hour prior to testing. Results showed that the fifteen minute systolic BP readings were significantly higher in the three energy drink trials (163.87, 166.47, and

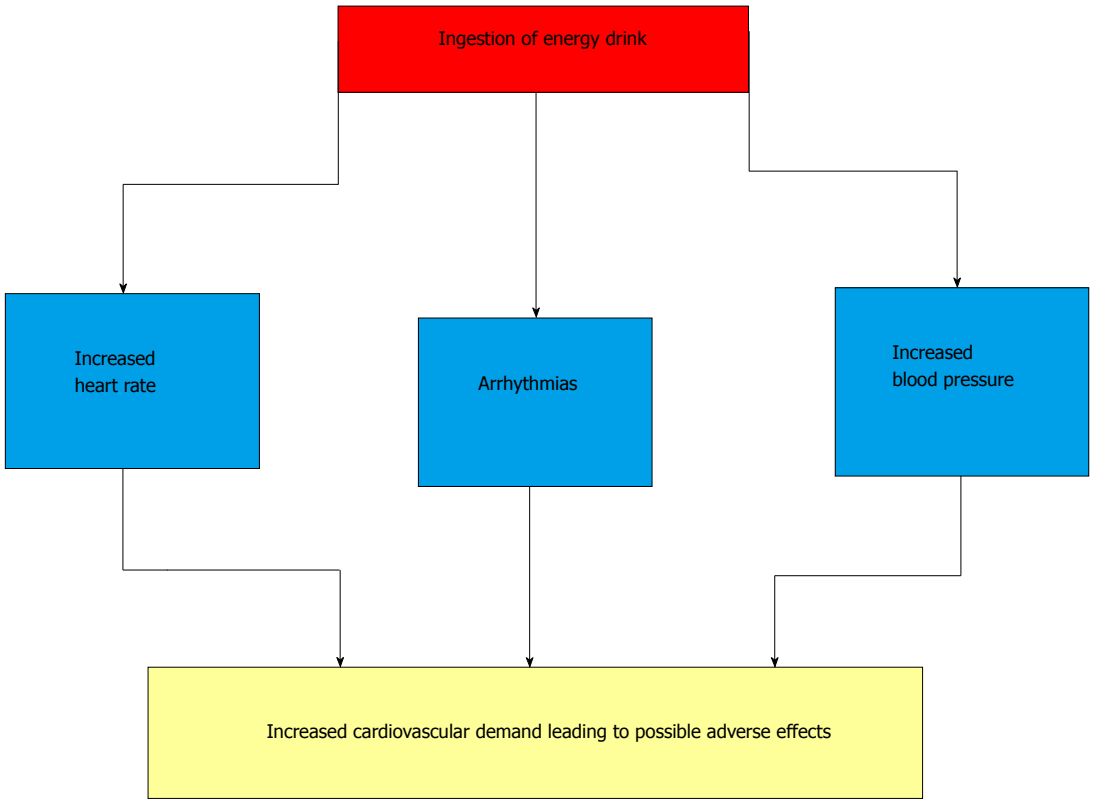

Figure 1 Effects of energy drinks on the cardiovascular system.

165.00) compared to the placebo trials (156)[12]. Other studies have found the same effect as well. Elitok *et al*[13] studied 50 young, healthy subjects and found that 2 h after consumption of 355 mL of Red Bull their systolic blood pressure increased from 112 to 121 mmHg, and diastolic blood pressure 73 to 76 mmHg. Grasser *et al*[14] conducted a randomized crossover study of twenty-five young non-obese and healthy subjects and showed that both systolic and diastolic blood pressure increased as a result of Red Bull consumption. The water control load did not. The study also showed increases in cerebrovascular resistance and breathing frequency, in addition to decreases in cerebral blood flow velocity and end-tidal carbon dioxide[14].

A recent comprehensive and systematic review of case studies related to EDs and their adverse health effects has found that the most common adverse events affect the neurological and cardiovascular systems. The neurological effects were most commonly seizures but also included neuro psychotic agitation, aggressive behavior, and suicidal ideation. That may be because caffeine and taurine are known psychoactive agents. The cardiac related events included reports of: Arrhythmias (highest percent 35% with the others being rare), coronary vasospasm, aortic aneurysm dissection, cardiac arrest, QT prolongation, acute cardiomyopathies, accelerated hypertension, reversible postural tachycardia syndrome, acute coronary thrombosis, and ST-elevation myocardial infarction. The authors attribute the cardiovascular adverse effects to the ingredients in ED, such as caffeine and taurine which have shown to increase platelet aggregation, disturb the endothelial function, and possibly causing vasospasm in association with hypertension[15]. Although there has been a link between energy drink consumption and platelet aggregation and endothelial dysfunction, the exact agent that is causing the effects is still unknown[16]. It should be noted that many of the adverse events described in these case reports have been linked to haphazard use of ED's and ED use combined with alcohol and other substances. Thus, emergency department case reports offer a hurdle to clearly understanding the adverse effects of EDs alone.

Another study was conducted with fifteen healthy adults. Their blood pressures were taken after abstaining from caffeine for 48 h, and, baseline BP, HR, and electrocardiographic (ECG) parameters were measured. Participants were asked to consume 500 mL of an energy drink and measurements were repeated 30 min, 1 h, 2 h, 3 h, and 4 h later, then drank 500 mL of energy drink daily for the next 5 d and measurements taken again on the final day. No significant ECG changes were noted, yet HR and SBP measurements increased by 5-7 beats/min and 10 mmHg, respectively. The cardiovascular effects were greater after five days of consumption than after the first day of consumption[17].

Another study enrolled fourteen volunteers, who completed a three-session study. In each session,

they received a 2oz. 5-h Energy shot, 2oz. Ocean Spray™ Diet Cranberry Juice as the placebo, or no drink with BP readings measured each hour. The energy shot condition showed diastolic BP readings that were significantly higher when compared to both the no drink and placebo drink conditions. Interestingly, it was also significantly higher at 240 and 360 min when compared to 60 min. There was no difference in BP between the placebo and no drink[5].

Physiologic effects on heart rhythm and induction of arrhythmia

A number of documented cases correlated the consumption of energy drinks to the development of atrial fibrillation such as: Atrial fibrillation in a 16-year-old Caucasian boy after consuming an unknown amount of Red Bull™ mixed with vodka[18]. A case of atrial fibrillation in a patient with dilated cardiomyopathy that experienced seizures after the cessation of his excessive caffeine consumption[19], and, atrial fibrillation in a 14-year-old Caucasian boy after an athletic event where he consumed an unknown amount of energy drink. He noted that he felt the same fluttering feeling 5 d before as well when he ingested a Red Bull™[18]. It is noteworthy that in all of such cases, there is a high suspicion for the excessive consumption of the beverages as the causal event.

CAFFEINE CONTENT AND DOSE

The caffeine content of energy drinks has been the center of the controversy, as it is widely believed that most such products contain a significantly higher concentration of caffeine than what is found in an average cup of coffee. The cardiovascular effects of caffeine have been heavily studied. Caffeine's inotropic effect on the heart muscle has been long looked at with suspicion as a possible culprit for heart disease in some people[20]. The last couple of decades saw coffee be linked with various harmful effects such as hypertension, gastric ulcers, palpitations, anxiety, tremulousness, and, ultimately, heart disease[21-23]. Hence, caffeine has an essential role in understanding the possible dangers of energy drinks.

In healthy individuals, caffeine, a methylxanthine, increases sympathetic nerve activity. Caffeine's molecular mechanism lies in its competitive inhibition of phosphodiesterase. This results in an elevation in myocardial cyclic AMP and, as a consequence, the positive inotropic action on the myocardium. On the other hand, the inhibition of adenosine receptors prevents the negative inotropic effect elicited by adenosine, namely, blocking the vasodilatory effect of adenosine and adenosine's inhibitory effects in platelet aggregation, catecholamine levels, renin release, and lipolysis. Thus, acute caffeine administration may increase blood pressure and increase levels of plasma catecholamine, renin, and free fatty acid[24].

As noted above, there is an extensive amount of literature that reveals that caffeine moderately increases blood pressure and heart rate[25-28] and also linked to a drop in myocardial blood flow[29,30]. However, caffeine has also been shown to have some positive benefits as well. One study showed that caffeine consumption was associated with a significant increase in flow-mediated dilation and a decrease in hs-CRP level in healthy volunteers and volunteers with coronary artery disease alike. It is noteworthy that these positive effects in endothelial dysfunction and inflammation were not seen with nitroglycerin application[31]. While these results seem promising, other studies have found negative effects that caffeine may have on endothelial function, such as a study conducted by Papamichael *et al*[32] they found that after ingestion of 80 mg of caffeine by healthy individuals, flow-mediated dilation was decreased in these individuals, most acutely in the first hour after ingestion. These results may not come as a surprise, as caffeine has been known to promote endothelial dysfunction through sympathetic activation[33].

A large prospective study followed 130054 members of a healthcare plan in Northern California gathering subjects from 1978 to 1985 and following them until 2008 to note the amount of coffee consumed by each individual and whether that added a risk for hospitalization for arrhythmias or any other cardiomyopathy. Results showed a strong inverse relationship of coffee consumption to risk of hospitalization for arrhythmia. The inverse relationship was consistent in men, women, whites, blacks, and persons younger or older than 60 years old at baseline[34]. This result shows that participants who consumed more cups of coffee generally were significantly less likely to develop cardiac arrhythmias. This shows the reverse of the idea traditionally held of increased caffeine consumption leading to more cardiac arrhythmias. Additionally, a comprehensive literature review dealing with the effects of habitual caffeine consumption on the cardiovascular system found that moderate consumption resulted in beneficial to neutral effects[35].

There is evidence, however, that point to caffeine's possible adverse effects especially when consumed at high doses. Toxic doses may affect conductance and refractoriness on the heart, which results in the development of various arrhythmias[36]. Symptoms of caffeine overdose also include palpitation, hypertension, irritability, insomnia, tremors, and seizures. In addition, the hypertensive effects of caffeine should not be overlooked as they may lead to hazardous cardiovascular events. The HARVEST study found that when after adjusting for possible confounding variables, cardiovascular events were more common among coffee drinkers than non-coffee drinkers. The authors suggested that hypertensive patients should be discouraged from drinking coffee[6].

Table 1 Caffeine concentration in common drinks

Caffeinated beverage	Amount of caffeine/drink, mg
5-h energy™ bottle	215
Arizona Iced Black Tea (16oz)	30
Bang Energy (16oz)	357
Caffeine Powder (1/16 Tsp.)	200
Coca Cola, Coke Zero, Diet Pepsi (12oz)	34
Dannon Coffee Yogurt (6oz)	30
Dunkin Donuts™ Medium Brewed Coffee (14oz)	178
Dunkin Donuts™ Medium Latte (14oz)	97
FDA official limit for cola and pepper soft drinks(12oz)	71
Herbal Tea (8oz)	0
Lipton Decaffeinated Black Tea (8oz)	5
Maxwell House Decaf Ground Coffee (2 Tbs. makes 12oz)	2-10
Maxwell House Light Ground Coffee (2 Tbs. makes 12oz)	50-100
Monster Energy™ (16oz)	160
Mountain Dew (12oz)	54
Pepsi (12oz)	38
Red Bull™ (8.4oz)	80
Rockstar™ (16oz)	160
Snapple Lemon Tea (16 oz)	37
Starbucks Grande Chai Latte (16oz)	95
Starbucks Hot Chocolate (16oz)	25
Starbucks Refreshers Can (12oz)	50
Starbucks™ Grande Caffe Americano (16oz)	225
Starbucks™ Grande Caffe Mocha (16oz)	175
Starbucks™ Grande Coffee Frapuccino (16oz)	95
Starbucks™ Grande Ice coffee (16oz)	165

There is a widespread belief that caffeine may be arrhythmogenic in those who regularly consume it. However, a large-scale Danish study did not find a higher risk for atrial fibrillation/flutter with different amounts of caffeine consumed[37]. In addition, the stimulant effects of caffeine seems to vary amongst individuals, in fact, the degree of tolerance and dependence to it is likely heritable and may be linked to polymorphisms[38].

Two comprehensive meta-analyses both determined that caffeine is unlikely to promote cardiovascular disease. In fact, the opposite may be true. The first review, conducted by Cheng *et al*[39] found an inverse relation was found between habitual caffeine intake and risk of atrial fibrillation. For every 300 mg per day increment in habitual caffeine intake, incidence of AF was found to drop by 6%. One explanation for these results is caffeine's association with lower risks of obesity, and metabolic disease. Thus, adverse cardiovascular effects of caffeine seem to represent itself with a J-shaped curve, with higher doses increasing the risks of heart disease, and normal doses proving to be beneficial[40].

The discrepancies in these studies can be difficult to reconcile although some of the variation in results may be attributed to differences in study design, varied caffeine dosages administered, and different study cohorts. Most studies do an inclusion criteria exercise for their cohorts. However, many did not take into account the regular coffee consumption of volunteers prior to the study. This is important because coffee metabolism is extremely variable in humans; thus, the effects of caffeine are not uniform. The half-life is 4.9 h, however absorption rates are largely based on the individual's genes, age, sex, liver health, and drug uptake, such as use of oral contraception, antidepressants, and antiarrhythmics, as well as their tolerance to the stimulant[41]. Caffeine is primarily metabolized through the liver's cytochrome P450 1A2 (CYP1A2) enzyme and defects in such an enzyme have been implicated in the population's variation in metabolism and half-life. Hence, genetic polymorphisms in the CYP1A2 pathway may explain some of the inconsistencies in studies of coffee and its effects on health[42].

To examine the caffeine amounts, Table 1 shows the caffeine concentrations of some popular drinks at Starbucks™ and Dunkin Donuts™ along with some of the most popular caffeine containing drinks[43]. Note that all EDs or energy shots surpass the FDA official soft drink concentration limit of 71 mg per twelve-ounce drink, sometimes by over triple the amount. According to the Mayo Clinic and the US food and Drug Administration up to 400 mg of caffeine a day appears to be safe for most healthy adults[44,45]. One study that supports this quantity mentions that maximum safe caffeine intake for pregnant women, children, and those taking medications is still undetermined[9,46]. Unfortunately, proper labeling has also been an issue, with companies reportedly falsely labeling caffeine content on their products, and

misguiding consumers[47].

OTHER ACTIVE INGREDIENTS IN ENERGY DRINKS AND THEIR ADDED EFFECTS

Taurine

Taurine is a derivative of the amino acid cysteine, and is found in high quantities in heart and skeletal muscle[48]. It is added in a large number of energy drinks such as 5-h energy™ and Red Bull™. Although taurine is considered an essential nutrient for humans, clinical studies evaluating the effects of taurine are limited. Taurine has been shown to be beneficial in improving the lipid profile by increasing the transcription of CYP7A1, an important enzyme in bile conjugation[49], as well increasing the liver's LDL uptake and up-regulation of LDL receptors[50]. Its supplementation has also been linked with a decrease in blood pressure possibly through the attenuation of angiotensin Ⅱ, which causes vasoconstriction[51] or by "enhancing" the kinin-kallikrein system, which normally causes vasodilation[52]. An ethnic Chinese study found an inverse correlation between twenty-four hour taurine excretion and diastolic blood pressure in Han (the major Chinese ethnic group) individuals and a decrease in both systolic and diastolic BPs in Tibetan subjects when consumed[53]. Similarly, there was a significant decrease in systolic and diastolic BPs in 19 borderline hypertensive subjects[54].

In addition, taurine deficiency was found to be associated with a decrease in the sensitivity of the cardiac muscle to Ca^{2+}, and, hence, a decreased inotropic capability of the organ[48]. This may be the reason for the supplements alleged boost in physical performance through an improved blood supply to the rest of the organs, specifically the musculoskeletal system. Interestingly, concentration of taurine have been found to be higher in the left ventricular muscle of hearts of patients who died of chronic congestive heart failure than that of patients who died of other causes and had no cardiac pathology[55]. The study hints that taurine may, in fact, have an inotropic effect which may shed some light on the cardiovascular adverse effects of energy drinks.

Certain studies have compared the effects of energy drinks containing just caffeine, and those containing caffeine and taurine. One study randomized nine volunteers to receive either an ED containing 80 mg of caffeine and 1000 mg of taurine or a control that contained 80 mg of caffeine solution in water. They were asked to consume their respective drink every 3-4 h for a single day. Mean 24-h systolic blood pressure, diastolic blood pressure, and mean arterial pressure recordings were significantly higher in the ED group than in the control (123.2 mmHg *vs* 117.4 mmHg, 73.6 mmHg *vs* 68.2 mmHg, 90.1 mmHg *vs* 84.8 mmHg, respectively)[56]. Another study asked 13 athletes to ingest either Red Bull, a similar caffeinated drink without taurine, or a placebo prior to performance of exhaustive endurance exercises. ECGs performed before ingestion, before exercise, after ingestion, during the recovery period showed that the only significant increase in stroke volume during the recovery period was the group that consumed taurine containing Red Bull. This study suggests that taurine and caffeine may interact together to increase cardiac contractility[57]. A third study explored the peak systolic strain in 32 healthy individuals at baseline, and one hour after consumption of an ED containing caffeine and taurine, or just caffeine. While the drink with caffeine did not seem to have any significant cardiovascular effects shown by magnetic resonance imagine, those that ingested the combination of caffeine and taurine had a significant increase in peak systolic strain[58].

Schaffer *et al*[59] conducted a comprehensive literature review regarding the interaction between taurine and caffeine and in agreement with the European Union's Scientific Committee on Food, they concluded that taurine should neutralize several untoward effects of caffeine excess. They noted that the physiological functions of taurine appear to be inconsistent with the adverse cardiovascular symptoms associated with excessive consumption of beverages containing caffeine and taurine.

B vitamins

Referred to as vitamin B complex, the eight B vitamins, thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine hydrochloride (B6), biotin (B7), inositol (B8), and cyanocobalamin (B12), act as coenzymes for proper cell function, especially mitochondrial function and energy production. Thus, some believe that B vitamins may increase energy expenditure[60]. One study has shown lower fat mass in men who regularly consumed multivitamins[61]. Energy drinks often contain a large quantity of B-group vitamins, often at larger doses than the recommended daily intake for healthy individuals.

Studies have shown that high dietary intakes of folate and vitamin B6 has been linked with reduced risk of mortality from stroke, coronary heart disease, and heart failure[62]. B vitamins have also been shown to reduce levels of the amino acid homocysteine whose elevation have been linked to numerous comorbidities including pregnancy complications, cognitive impairment and mental disorders, as well as cardiovascular risks[63-65].

A meta-analysis established that while B vitamin supplementation the B vitamin reduced homocysteine levels and has a significant protective effect on stroke, no benefit was found to reduce cardiovascular disease, myocardial infarction, coronary artery disease,

cardiovascular death, or all-cause mortality[66].

Guarana

Paullinia cupana, also known as guarana, is a South American plant that has been mentioned as early as 1872 for the treatment of "Sick-Headache"[67]. The Amazonians have used the seeds of its fruit to increase awareness and energy[68]. Guarana's stimulant effect is due to its similar chemical composition to that of caffeine. There is 2%-4.5% caffeine in the guarana seeds, compared to 1%-2% in the coffee bean[69]. The effect of guarana is not yet known. Whether it is of additive or synergistic effect when combined with caffeine is not clear. Guarana in a 16 ounce energy drink ranges from 1.4 mg to as much as 300 mg. The FDA generally recognizes guarana as safe, although there are no established dosages and it is unclear how much guarana is in each drink because many companies do not list a milligram amount. Therefore, it should be assumed that the amount of caffeine in the products is, in reality, larger than the amount of caffeine noted especially when guarana is present. It is not surprising that young adults have been admitted to emergency departments with cardiovascular adverse effects after excessive ingestion of guarana-based EDs[70].

L-carnitine

A meta-analysis on the effect of the L-carnitine supplement on the cardiovascular system found a 40% reduction in angina (RR, 0.60; 95%CI, 0.50-0.72; $P < 0.00001$; $I^2 = 0\%$). Compared with placebo or control, L-carnitine was found to be associated with a highly significant 65% reduction in ventricular arrhythmias (RR = 0.35; 95%CI: 0.21-0.58, $P < 0.0001$, $I^2 = 0\%$)[71]. An increase in cardiac output after intravenous administration of L-carnitine in normotensive coronary artery disease patients has also been observed[72]. Another study showed that L-carnitine supplementation increased the left ventricular ejection fraction in studied individuals. The mean percent of increase of ejection fraction in the L-carnitine group was 12.5% ± 8.3% ($P < 0.01$), while the control group had an increase of ejection fraction of 6.1% ± 4.3% ($P < 0.01$)[73]. In addition, the supplementation of L-carnitine has been shown to decrease left ventricular remodeling in post-myocardial infarction patients[74]. However, Koeth *et al*[75] recently found a possible link of L-carnitine in red meat with cardiovascular disease through the development of atherosclerosis. This effect may simply be due to the long acknowledged negative effect of red meat on the cardiovascular system instead of L-carnitine itself.

L-carnitine is a naturally occurring amino acid made predominantly by the liver and kidneys. It is involved in B-oxidation of fatty acids and is thus linked to changes in metabolism and energy levels. It is commonly added to energy drinks to help promote muscle function and physical performance. It is found in energy drinks such as Monster™ and Rockstar™ energy drinks.

L-carnitine's popularity in EDs is due to its possible ability to burn more fat and increase endurance during exercise, however, those claims remain elusive. Some data has indicated that L-carnitine plays an important role in the prevention of cellular damage and positively affects recovery from exercise stress. Uptake of L-carnitine by blood cells has been implicated in stimulation of hematopoiesis, a dose-dependent inhibition of collagen-induced platelet aggregation; and the prevention of programmed cell death in immune cells. Carnitine was recently shown to have direct effects in the regulation of gene expression and is potentially involved in modulating intracellular fatty acid concentration. Hence, there is evidence for a positive effect of L-carnitine supplementation. It may be especially beneficial in training and recovery from strenuous exercise[76]. In high doses, L-carnitine has been shown to have a side effect of nausea, vomiting, abdominal pain, and diarrhea; in addition, it has been associated with seizures in patients with no known disease and to increase seizure frequency in patients with seizure disorder[9]. However, as with ginseng, the amount of L-carnitine in energy drinks is likely not high enough to be of concern.

Ginseng

This East Asian herb is one of the most popular herbal supplements in the world and has also been a popular additive in EDs. The claims about ginseng range far and wide-reducing stress, curing diabetes, insomnia, erectile dysfunction, improving memory, and increasing stamina are all purported benefits of the herb. However, very few claims are rooted in scientific research. A recent review concluded that evidence of enhanced physical performance after ginseng administration in well-designed investigations remains to be demonstrated[77].

In 2013, one Mayo Clinic study did show that after eight weeks of taking 2000 milligrams of pure American ginseng root in a capsule, patients undergoing cancer treatment found a sudden jump in the general energy levels reported by the group on ginseng when compared to the placebo control group[78].

Interestingly, several studies in rats have results suggesting that oral administration of ginseng root may increase insulin sensitivity and help with weight loss. Researchers at the University of Chicago administered daily intraperitoneal injections of Panax ginseng berry extract to rats and on day 12, extract-treated *ob*/*ob* mice became normoglycemic and were found to have significantly improved glucose tolerance. A more than twofold increase in the rate of insulin-stimulated glucose disposal in treated *ob*/*ob* mice was noted in hyperinsulinemic-euglycemic clamp study. The mice also lost a significant amount of weight which was

believed to be associated with the reduced food intake and the increase in body temperature and energy expenditure. Other studies revealed that ginsenoside Re plays a significant role in antihyperglycemic action. Interestingly, this antidiabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other components in the extract have distinct pharmacological mechanisms on energy metabolism. Additionally, plasma cholesterol levels were notably reduced following the treatment with the extract[79].

Excessive amounts of ginseng ingestion may cause diarrhea, vaginal bleeding, headache, vertigo, mania, hypertension, rashes, insomnia, irritability, Stevens-Johnson syndrome, and agranulocytosis. However, some of these symptoms may be related to contaminants, such as phenylbutazone and aminopyrine that are used in its production[6]. However, the amounts of ginseng found in EDs are thought to be less than the amount needed to deliver the suggested therapeutic benefits or cause adverse events[80].

Glucuronolactone

Glucuronolactone is a glucose derivative, metabolized in the liver. In the sixties, the Japanese were particularly interested in its performance enhancing properties. They conducted one published study by injecting glucuronolactone, glucose, glycogen, and some other substances directly into the gut of lab rats, and recording the rats' ability to swim 30 min post injection. They repeated the procedure three times. In two of the three trials, the animals injected with glucuronolactone were able to swim longer than those injected with the other substances. The study also noted that the human equivalent of the dose would be between 1 and 2 g of glucuronolactone compared to the 600 mg found in a can of Red Bull[81]. These results may be due to glucuronolactone detoxification effects as supplementation with glucuronolactone may favor the body's natural defense mechanism for eliminating carcinogens and tumor promoters and their effects[82].

Glucuronolactone has shown to act as an anti-platelet aggregative compound[83], however, this outcome has not been proven to be effective when mixed in energy drinks, as after consumption an overall increase in platelet aggregation appears without any apparent effect of platelet anti-aggregation of the glucuronolactone[16]. There has been minimal suggested significant contribution towards energy by glucuronolactone on humans in the scientific literature and, therefore, no definitive conclusion can be made of its safety[84].

OVERALL ASSESSMENT

The increasing number of energy drink and caffeine-related overdoses clearly shows that there seems to be a real risk for adverse health effects such as arrhythmias. However, under moderate use and without combining other stimulants or alcohol, the lack of a similar number of case reports makes the risk for such side effects seem negligible. It is noteworthy that a large number of serious health risks resulted were due to overconsumption of the products or their ingestion in a short period of time. Therefore, it may well be important for energy drink companies to place warnings on their products to avoid such habits.

The exact amounts and concentrations that are ideal in order to minimize the health risks are largely unknown. Patients with underlying illnesses such as hepatic failure or cardiomyopathy should likely avoid such products or, at least, be cautious by consuming small amounts. In addition, since there seems to be variation amongst individuals in the enzymatic activity of CYP1A2 and since testing for such enzymatic activity is not routinely performed, it is of great importance for each consumer to cease consuming the energy drinks if symptoms of an overdose develop. Producers should place a warning that includes such symptoms.

As for the constituents of the energy drinks themselves, the concentrations of caffeine seem to be comparable or even lower than many popular coffee drinks making the amount of caffeine itself an unlikely reason to not consume the products. In fact, medical research has shown that moderate consumption of caffeine is strongly related to a reduced risk of arrhythmias.

As for taurine and L-carnitine, the medical literature shows an overall positive health effect especially for the cardiovascular system, hence, making it unlikely that they can cause harm to that same system. In fact, it may be reasonable to consider those two compounds for future supplementation to those at risk for hyperlipidemia, hypertension, and cardiomyopathy. Guarana, on the other hand, may have a synergistic caffeine-like effect added to the caffeine already in these products and more information is needed on their combined effect.

CONCLUSION

The last decade has seen an exponential increase in the number of energy drink products as well as the number of reported cases of arrhythmias and other health hazards caused by their consumption. Our review has found that the vast majority of the cases were due to excessive consumption of the drinks in a short period of time or when co-ingested with other stimulants such as alcohol and indicates that such drinks may be relatively safe when consumed moderately and separately. Additionally, the research covering the components of the beverages, such as caffeine, taurine, L-carnitine, glucuronolactone, ginseng, and guarana, seems to have a neutral to positive health effect unlike previously thought. However, it may be important for energy drink

producers to place warning labels of symptoms associated with an overdose in order to promote their recognition. Until the FDA sanctions these energy drink products, it is strongly encouraged that individuals research energy drink consumption and consult their physician in order to ensure safe consumption. Also, those with underlying cardiovascular disease should be careful by limiting the amount consumed or avoiding altogether, as they may be at increased risk for arrhythmias or other cardiovascular events.

With the exception of the effects of caffeine, the ingredients in energy drinks have not been thoroughly studied to confirm the cardiovascular safety or the proclaimed energy-boosting benefits. There is an overwhelming lack of evidence to substantiate claims that components of EDs, contribute to the enhancement of physical or cognitive performance. Additional well-designed, randomized, placebo-controlled studies are needed in order to assess claims made for these products and further elucidate potential adverse effects.

REFERENCES

1 **Reissig CJ**, Strain EC, Griffiths RR. Caffeinated energy drinks--a growing problem. *Drug Alcohol Depend* 2009; **99**: 1-10 [PMID: 18809264 DOI: 10.1016/j.drugalcdep.2008.08.001]

2 **Drug Abuse Warning Network**, 2011: National Estimates of Drug-Related Emergency Department Visits. SAMHSAgov. [accessed 2017 Apr 14]. Available from: URL: https://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.pdf

3 **Kim IK**, Kim KM. Energy drink consumption patterns and associated factors among nursing students: a descriptive survey study. *J Addict Nurs* 2015; **26**: 24-31 [PMID: 25761160 DOI: 10.1097/JAN.0000000000000061]

4 **Wesnes KA**, Barrett ML, Udani JK. An evaluation of the cognitive and mood effects of an energy shot over a 6h period in volunteers: a randomized, double-blind, placebo controlled, cross-over study. *Appetite* 2013; **67**: 105-113 [PMID: 23587521 DOI: 10.1016/j.appet.2013.04.005]

5 **Marczinski CA**, Stamates AL, Ossege J, Maloney SF, Bardgett ME, Brown CJ. Subjective State, Blood Pressure, and Behavioral Control Changes Produced by an "Energy Shot" *J Caffeine Res* 2014; **4**: 57-63 [PMID: 25054080 DOI: 10.1089/jcr.2014.0005]

6 **Malinauskas BM**, Aeby VG, Overton RF, Carpenter-Aeby T, Barber-Heidal K. A survey of energy drink consumption patterns among college students. *Nutr J* 2007; **6**: 35 [PMID: 17974021 DOI: 10.1186/1475-2891-6-35]

7 **Cotter BV**, Jackson DA, Merchant RC, Babu KM, Baird JR, Nirenberg T, Linakis JG. Energy drink and other substance use among adolescent and young adult emergency department patients. *Pediatr Emerg Care* 2013; **29**: 1091-1097 [PMID: 24076613 DOI: 10.1097/PEC.0b013e3182a6403d]

8 **Nordt SP**, Vilke GM, Clark RF, Lee Cantrell F, Chan TC, Galinato M, Nguyen V, Castillo EM. Energy drink use and adverse effects among emergency department patients. *J Community Health* 2012; **37**: 976-981 [PMID: 22367607 DOI: 10.1007/s10900-012-9549-9]

9 **Seifert SM**, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics* 2011; **127**: 511-528 [PMID: 21321035 DOI: 10.1542/peds.2009-3592]

10 **George J**, Murphy T, Roberts R, Cooksley WG, Halliday JW, Powell LW. Influence of alcohol and caffeine consumption on caffeine elimination. *Clin Exp Pharmacol Physiol* 1986; **13**: 731-736 [PMID: 3802578 DOI: 10.1111/j.1440-1681.1986.tb02414.x]

11 **Grasser EK**, Dulloo AG, Montani J-P. Cardiovascular and Cerebrovascular Effects in Response to Red Bull Consumption Combined With Mental Stress. *Am J Cardiol* 2015; **115**: 183-189 [DOI: 10.1016/j.amjcard.2014.10.017]

12 **Peveler WW**, Sanders GJ, Marczinski CA, Holmer B. Effects of Energy Drinks on Economy and Cardiovascular Measures. *J Strength Cond Res* 2017; **31**: 882-887 [PMID: 27386963 DOI: 10.1519/JSC.0000000000001553]

13 **Elitok A**, Öz F, Panc C, Sarıkaya R, Sezikli S, Pala Y, Bugan ÖS, Ateş M, Parıldar H, Ayaz MB, Atıcı A, Oflaz H. Acute effects of Red Bull energy drink on ventricular repolarization in healthy young volunteers: a prospective study. *Anatol J Cardiol* 2015; **15**: 919-922 [PMID: 25868042 DOI: 10.5152/akd.2015.5791]

14 **Grasser EK**, Yepuri G, Dulloo AG, Montani JP. Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr* 2014; **53**: 1561-1571 [PMID: 24474552 DOI: 10.1007/s00394-014-0661-8]

15 **Ali F**, Rehman H, Babayan Z, Stapleton D, Joshi DD. Energy drinks and their adverse health effects: A systematic review of the current evidence. *Postgrad Med* 2015; **127**: 308-322 [PMID: 25560302 DOI: 10.1080/00325481.2015.1001712]

16 **Worthley MI**, Prabhu A, De Sciscio P, Schultz C, Sanders P, Willoughby SR. Detrimental effects of energy drink consumption on platelet and endothelial function. *Am J Med* 2010; **123**: 184-187 [PMID: 20103032 DOI: 10.1016/j.amjmed.2009.09.013]

17 **Steinke L**, Lanfear DE, Dhanapal V, Kalus JS. Effect of "energy drink" consumption on hemodynamic and electrocardiographic parameters in healthy young adults. *Ann Pharmacother* 2009; **43**: 596-602 [PMID: 19299320 DOI: 10.1345/aph.1L614]

18 **Di Rocco JR**, During A, Morelli PJ, Heyden M, Biancaniello TA. Atrial fibrillation in healthy adolescents after highly caffeinated beverage consumption: two case reports. *J Med Case Rep* 2011; **5**: 18 [PMID: 21247417 DOI: 10.1186/1752-1947-5-18]

19 **Peake STC**, Mehta PA, Dubrey SW. Atrial fibrillation-related cardiomyopathy: a case report. *J Med Case Rep* 2007; **1**: 111 [DOI: 10.1186/1752-1947-1-111]

20 **Lin CI**, Vassalle M. Role of calcium in the inotropic effects of caffeine in cardiac Purkinje fibers. *Int J Cardiol* 1983; **3**: 421-434 [PMID: 6885189 DOI: 10.1016/0167-5273(83)90113-4]

21 **Shapiro RE**. Caffeine and headaches. *Neurol Sci* 2007; **28** Suppl 2: S179-S183 [PMID: 17508167 DOI: 10.1007/s10072-007-0773-5]

22 **Sepkowitz KA**. Energy drinks and caffeine-related adverse effects. *JAMA* 2013; **309**: 243-244 [PMID: 23330171 DOI: 10.1001/jama.2012.173526]

23 **Shirlow MJ**, Mathers CD. A study of caffeine consumption and symptoms; indigestion, palpitations, tremor, headache and insomnia. *Int J Epidemiol* 1985; **14**: 239-248 [PMID: 3874838 DOI: 10.1093/ije/14.2.239]

24 **Mesas AE**, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. *Am J Clin Nutr* 2011; **94**: 1113-1126 [PMID: 21880846 DOI: 10.3945/ajcn.111.016667]

25 **Astorino TA**, Martin BJ, Schachtsiek L, Wong K. Caffeine ingestion and intense resistance training minimize postexercise hypotension in normotensive and prehypertensive men. *Res Sports Med* 2013; **21**: 52-65 [PMID: 23286422 DOI: 10.1080/15438627.2012.738443]

26 **Phan JK**, Shah SA. Effect of caffeinated versus noncaffeinated energy drinks on central blood pressures. *Pharmacotherapy* 2014; **34**: 555-560 [PMID: 24644139 DOI: 10.1002/phar.1419]

27 **Lemery R**, Pecarskie A, Bernick J, Williams K, Wells GA. A prospective placebo controlled randomized study of caffeine in patients with supraventricular tachycardia undergoing electrophysiologic testing. *J Cardiovasc Electrophysiol* 2015; **26**: 1-6 [PMID: 25081280 DOI: 10.1111/jce.12504]

28 **Noguchi K**, Matsuzaki T, Sakanashi M, Hamadate N, Uchida T, Kina-Tanada M, Kubota H, Nakasone J, Sakanashi M, Ueda S,

Masuzaki H, Ishiuchi S, Ohya Y, Tsutsui M. Effect of caffeine contained in a cup of coffee on microvascular function in healthy subjects. *J Pharmacol Sci* 2015; **127**: 217-222 [PMID: 25727960 DOI: 10.1016/j.jphs.2015.01.003]

29 **Pelchovitz DJ**, Goldberger JJ. Caffeine and cardiac arrhythmias: a review of the evidence. *Am J Med* 2011; **124**: 284-289 [PMID: 21435415 DOI: 10.1016/j.amjmed.2010.10.017]

30 **Pendleton M**, Brown S, Thomas CM, Odle B. Potential toxicity of caffeine when used as a dietary supplement for weight loss. *J Diet Suppl* 2013; **10**: 1-5 [PMID: 23374013 DOI: 10.3109/19390211.2012.758215]

31 **Shechter M**, Shalmon G, Scheinowitz M, Koren-Morag N, Feinberg MS, Harats D, Sela BA, Sharabi Y, Chouraqui P. Impact of acute caffeine ingestion on endothelial function in subjects with and without coronary artery disease. *Am J Cardiol* 2011; **107**: 1255-1261 [PMID: 21349479 DOI: 10.106/j.amjcard.2010.12.035]

32 **Papamichael CM**, Aznaouridis KA, Karatzis EN, Karatzi KN, Stamatelopoulos KS, Vamvakou G, Lekakis JP, Mavrikakis ME. Effect of coffee on endothelial function in healthy subjects: the role of caffeine. *Clin Sci* (Lond) 2005; **109**: 55-60 [PMID: 15799717 DOI: 10.1042/CS20040358]

33 **Nurminen ML**, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *Eur J Clin Nutr* 1999; **53**: 831-839 [PMID: 10556993 DOI: 10.1038/sj.ejcn.1600899]

34 **Klatsky AL**, Hasan AS, Armstrong MA, Udaltsova N, Morton C. Coffee, caffeine, and risk of hospitalization for arrhythmias. *Perm J* 2011; **15**: 19-25 [PMID: 22058665]

35 **O'Keefe JH**, Bhatti SK, Patil HR, DiNicolantonio JJ, Lucan SC, Lavie CJ. Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *J Am Coll Cardiol* 2013; **62**: 1043-1051 [PMID: 23871889 DOI: 10.1016/j.jacc.2013.06.035]

36 **Zulli A**, Smith RM, Kubatka P, Novak J, Uehara Y, Loftus H, Qaradakhi T, Pohanka M, Kobyliak N, Zagatina A, Klimas J, Hayes A, La Rocca G, Soucek M, Kruzliak P. Caffeine and cardiovascular diseases: critical review of current research. *Eur J Nutr* 2016; **55**: 1331-1343 [PMID: 26932503 DOI: 10.1007/s00394-016-1179-z]

37 **Frost L**, Vestergaard P. Caffeine and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005; **81**: 578-582 [PMID: 15755825]

38 **Temple JL**. Caffeine use in children: what we know, what we have left to learn, and why we should worry. *Neurosci Biobehav Rev* 2009; **33**: 793-806 [PMID: 19428492 DOI: 10.1016/j.neubiorev.2009.01.001]

39 **Cheng M**, Hu Z, Lu X, Huang J, Gu D. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. *Can J Cardiol* 2014; **30**: 448-454 [PMID: 24680173 DOI: 10.1016/j.cjca.2013.12.026]

40 **Mostofsky E**, Rice MS, Levitan EB, Mittleman MA. Habitual Coffee Consumption and Risk of Heart Failure: A Dose-Response Meta-Analysis. *Circulation: Heart Failure* 2012; **5**: 401-405 [DOI: 10.1161/circheartfailure.112.967299]

41 **Lozano RP**, García YA, Tafalla DB, Albaladejo MF. Cafeína: Un nutriente, un fármaco, o una droga de abuso. *Adicciones* 2007; **19**: 225-238 [DOI: 10.20882/adicciones.303]

42 **Aklillu E**, Djordjevic N, Carrillo JA, Makonnen E, Bertilsson L, Ingelman-Sundberg M. High CYP2A6 enzyme activity as measured by a caffeine test and unique distribution of CYP2A6 variant alleles in Ethiopian population. *OMICS* 2014; **18**: 446-453 [DOI: 10.1089/omi.2013.0140]

43 Caffeine Chart Center for Science in the Public Interest. [accessed 2017 Apr 14]. Available from: URL: https://cspinet.org/eating-healthy/ingredients-of-concern/caffeine-chart

44 **Mayo Clinic Staff**. Caffeine: How much is too much? 2017 March 8. [accessed 2017 Apr 14]. Available from: URL: http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20045678

45 **Nawrot P**, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on human health. *Food Addit Contam* 2003; **20**: 1-30 [PMID: 12519715 DOI: 10.1080/0265203021000007840]

46 **Higgins JP**, Babu KM. Caffeine reduces myocardial blood flow during exercise. *Am J Med* 2013; **126**: 730.e1-730.e8 [PMID: 23764265 DOI: 10.1016/j.amjmed.2012.12.023]

47 **Schwartz ND**. New York State Is Investigating Energy Drink Makers. *The New York Times*; 2012 August 28

48 **Eley DW**, Lake N, ter Keurs HE. Taurine depletion and excitation-contraction coupling in rat myocardium. *Circ Res* 1994; **74**: 1210-1219 [PMID: 8187287 DOI: 10.1161/01.RES.74.6.1210]

49 **Lam NV**, Chen W, Suruga K, Nishimura N, Goda T, Yokogoshi H. Enhancing effect of taurine on CYP7A1 mRNA expression in Hep G2 cells. *Amino Acids* 2006; **30**: 43-48 [DOI: 10.1007/s00726-005-0244-3]

50 **Murakami S**, Kondo Y, Toda Y, Kitajima H, Kameo K, Sakono M, Fukuda N. Effect of taurine on cholesterol metabolism in hamsters: up-regulation of low density lipoprotein (LDL) receptor by taurine. *Life Sci* 2002; **70**: 2355-2366 [PMID: 12150200 DOI: 10.1016/S0024-3205(02)01507-2]

51 **Schaffer SW**, Lombardini JB, Azuma J. Interaction between the actions of taurine and angiotensin II. *Amino Acids* 2000; **18**: 305-318 [PMID: 10949914 DOI: 10.1007/PL00010320]

52 **Kohashi N**, Katori R. Decrease of urinary taurine in essential hypertension. *Jpn Heart J* 1983; **24**: 91-102 [PMID: 6854956]

53 **Liu L**, Liu L, Ding Y, Huang Z, He B, Sun S, Zhao G, Zhang H, Miki T, Mizushima S, Ikeda K, Nara Y, Yamori Y. Ethnic and environmental differences in various markers of dietary intake and blood pressure among Chinese Han and three other minority peoples of China: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Hypertens Res* 2001; **24**: 315-322 [PMID: 11409657 DOI: 10.1291/hypres.24.315]

54 **Fujita T**, Ando K, Noda H, Ito Y, Sato Y. Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension. *Circulation* 1987; **75**: 525-532 [PMID: 3815764 DOI: 10.1161/01.CIR.75.3.525]

55 **Huxtable R**, Bressler R. Taurine concentrations in congestive heart failure. *Science* 1974; **184**: 1187-1188 [PMID: 4833255 DOI: 10.1126/science.184.4142.1187]

56 **Franks AM**, Schmidt JM, McCain KR, Fraer M. Comparison of the effects of energy drink versus caffeine supplementation on indices of 24-hour ambulatory blood pressure. *Ann Pharmacother* 2012; **46**: 192-199 [PMID: 22298600 DOI: 10.1345/aph.1Q555]

57 **Baum M**, Weiss M. The influence of a taurine containing drink on cardiac parameters before and after exercise measured by echocardiography. *Amino Acids* 2001; **20**: 75-82 [PMID: 11310932 DOI: 10.1007/s007260170067]

58 **Doerner JM**, Kuetting DL, Luetkens JA, Naehle CP, Dabir D, Homsi R, Nadal J, Schild HH, Thomas DK. Caffeine and taurine containing energy drink increases left ventricular contractility in healthy volunteers. *Int J Cardiovasc Imaging* 2015; **31**: 595-601 [PMID: 25425431 DOI: 10.1007/s10554-014-0577-7]

59 **Schaffer SW**, Shimada K, Jong CJ, Ito T, Azuma J, Takahashi K. Effect of taurine and potential interactions with caffeine on cardiovascular function. *Amino Acids* 2014; **46**: 1147-1157 [PMID: 24615238 DOI: 10.1007/s00726-014-1708-0]

60 **Williams MH**. Dietary Supplements and Sports Performance: Introduction and Vitamins. *Journal of the International Society of Sports Nutrition* 2004; **1**: 1 [DOI: 10.1186/1550-2783-1-2-1]

61 **Major GC**, Doucet E, Jacqmain M, St-Onge M, Bouchard C, Tremblay A. Multivitamin and dietary supplements, body weight and appetite: results from a cross-sectional and a randomised double-blind placebo-controlled study. *Br J Nutr* 2008; **99**: 1157-1167 [PMID: 17977472 DOI: 10.1017/s0007114507853335]

62 **Cui R**, Iso H, Date C, Kikuchi S, Tamakoshi A; Japan Collaborative Cohort Study Group. Dietary folate and vitamin b6 and B12 intake in relation to mortality from cardiovascular diseases: Japan collaborative cohort study. *Stroke* 2010; **41**: 1285-1289 [PMID: 20395608 DOI: 10.1161/STROKEAHA.110.578906]

63 **Bønaa KH**, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl*

J Med 2006; **354**: 1578-1588 [PMID: 16531614 DOI: 10.1056/NEJMoa055227]
64 **Wald NJ**, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326**: 1419 [PMID: 12829553 DOI: 10.1136/bmj.326.7404.1419]
65 **Verhaar MC**, Stroes E, Rabelink TJ. Folates and cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2002; **22**: 6-13 [PMID: 11788454 DOI: 10.1161/hq0102.102190]
66 **Huang T**, Chen Y, Yang B, Yang J, Wahlqvist ML, Li D. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. *Clin Nutr* 2012; **31**: 448-454 [PMID: 22652362 DOI: 10.1016/j.clnu.2011.01.003]
67 **Wilks S**. Guarana a Remedy for Sick-Headache. *Br Med J* 1872; **1**: 421 [PMID: 20746599]
68 **Smith N**, Atroch AL. Guaraná's journey from regional tonic to aphrodisiac and global energy drink. *Evid Based Complement Alternat Med* 2007; **5**: 5 [DOI: 10.1093/ecam/nem162]
69 **Bempong DK**, Houghton PJ, Steadman K. "The xanthine content of guarana and its preparations". *Int J Pharmacog* 1993; **31**: 175-181 [DOI: 10.3109/13880209309082937]
70 **Schimpl FC**, da Silva JF, Gonçalves JF, Mazzafera P. Guarana: revisiting a highly caffeinated plant from the Amazon. *J Ethnopharmacol* 2013; **150**: 14-31 [PMID: 23981847 DOI: 10.1016/j.jep.2013.08.023]
71 **DiNicolantonio JJ**, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Mayo Clin Proc* 2013; **88**: 544-551 [PMID: 23597877 DOI: 10.1016/j.mayocp.2013.02.007]
72 **Bartels GL**, Remme WJ, Pillay M, Schönfeld DH, Cox PH, Kruijssen HA, Knufman NM. Acute improvement of cardiac function with intravenous L-propionylcarnitine in humans. *J Cardiovasc Pharmacol* 1992; **20**: 157-164 [PMID: 1383625]
73 **Gürlek A**, Tutar E, Akçil E, Dinçer I, Erol C, Kocatürk PA, Oral D. The effects of L-carnitine treatment on left ventricular function and erythrocyte superoxide dismutase activity in patients with ischemic cardiomyopathy. *Eur J Heart Fail* 2000; **2**: 189-193 [PMID: 10856733 DOI: 10.1016/S1388-9842(00)00064-7]
74 **Iliceto S**, Scrutinio D, Bruzzi P, D'Ambrosio G, Boni L, Di Biase M, Biasco G, Hugenholtz PG, Rizzon P. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. *J Am Coll Cardiol* 1995; **26**: 380-387 [PMID: 7608438 DOI: 10.1016/0735-1097(95)80010-E]
75 **Koeth RA**, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013; **19**: 576-585 [PMID: 23563705 DOI: 10.1038/nm.3145]
76 **Karlic H**, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? *Nutrition* 2004; **20**: 709-715 [PMID: 15212755 DOI: 10.1016/j.nut.2004.04.003]
77 **Bahrke MS**, Morgan WP, Stegner A. Is ginseng an ergogenic aid? *Int J Sport Nutr Exerc Metab* 2009; **19**: 298-322 [PMID: 19574616 DOI: 10.1123/ijsnem.19.3.298]
78 **Barton DL**, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, McGinn TW, Stella PJ, Seeger GR, Sood A, Loprinzi CL. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst* 2013; **105**: 1230-1238 [PMID: 23853057 DOI: 10.1093/jnci/djt181]
79 **Attele AS**, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS. Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. *Diabetes* 2002; **51**: 1851-1858 [PMID: 12031973 DOI: 10.2337/diabetes.51.6.1851]
80 **Clauson KA**, Shields KM, McQueen CE, Persad N. Safety issues associated with commercially available energy drinks. *J Am Pharm Assoc* (2003) 2008; **48**: e55-63; quiz e64-7 [PMID: 18595815 DOI: 10.1331/JAPhA.2008.07055]
81 **Tamura S**, Tsutsumi S, Ito H, Nakai K, Masuda M. Effects of glucuronolactone and the other carbohydrates on the biochemical changes produced in the living body of rats by hard exercise. *Jpn J Pharmacol* 1968; **18**: 30-38 [PMID: 5302458 DOI: 10.1254/jjp.18.30]
82 **Zóltaszek R**, Hanausek M, Kiliańska ZM, Walaszek Z. [The biological role of D-glucaric acid and its derivatives: potential use in medicine]. *Postepy Hig Med Dosw* (Online) 2008; **62**: 451-462 [PMID: 18772850]
83 **Olas B**, Saluk-Juszczak J, Nowak P, Glowacki R, Bald E, Wachowicz B. Protective effects of D-glucaro 1,4-lactone against oxidative/nitrative modifications of plasma proteins. *Nutrition* 2007; **23**: 164-171 [PMID: 17234507 DOI: 10.1016/j.numecd.2007.02.016]
84 **Mets MA**, Ketzer S, Blom C, van Gerven MH, van Willigenburg GM, Olivier B, Verster JC. Positive effects of Red Bull® Energy Drink on driving performance during prolonged driving. *Psychopharmacology* (Berl) 2011; **214**: 737-745 [PMID: 21063868 DOI: 10.1007/s00213-010-2078-2]

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ORIGINAL ARTICLE

Randomized Clinical Trial

Randomized study comparing incidence of radial artery occlusion post-percutaneous coronary intervention between two conventional compression devices using a novel air-inflation technique

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Author contributions: Voon V performed data collection, analyzed and interpreted data, and wrote manuscript; Ayyaz Ul Haq M, Cahill C, Mannix K, Ahern C, Hennessy T, Arnous S performed and conducted data collection; Kiernan T contributed to the conception and design of study and wrote manuscript; all authors critically reviewed the manuscript and approved it.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of University Hospital Limerick, Dooradoyle, Limerick, Ireland.

Informed consent statement: All eligible patients gave written informed consent to participate in the study, prior enrollment.

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Abstract

AIM

To compare post-percutaneous coronary intervention (PCI) radial artery occlusion (RAO) incidence between two conventional radial artery compression devices using a novel air-inflation technique.

METHODS

One hundred consecutive patients post-PCI were randomized 1:1 to Safeguard or TR band compression devices. Post-radial sheath removal, each compression device was inflated with additional 2 mL of air above index bleeding point during air-filled device application and gradually down-titrated accordingly. RAO was defined as absence of Doppler flow signal performed at 24 h and at 6 wk post-PCI. Patients with missing data were excluded. Statistical significance was defined as $P < 0.05$.

RESULTS
All patients had 6F radial sheath inserted. No significant differences were observed between Safeguard Radial (*n* = 42) *vs* TR band (*n* = 42) in terms of age (63 ± 11 years *vs* 67 ± 11 years), clinical presentation (electives, *n* = 18 *vs n* = 16; acute coronary syndrome, *n* = 24 *vs n* = 26) and total procedural heparin (7778 ± 2704 IU *vs* 7825 ± 2450 IU). RAO incidence was not significantly different between groups at 24 h (2% *vs* 0%, *P* = 0.32) and 6 wk (0%, both).

CONCLUSION
Safeguard Radial and TR band did not demonstrate significant between-group differences in short-term RAO incidence. Lack of evidence of RAO in all post-PCI patients at 6 wk follow-up, regardless of radial compression device indicate advantage of using the novel and pragmatic air-inflation technique. Further work is required to more accurately confirm these findings.

Key words: Radial artery; Arterial occlusive disease; Cardiac catheterization

Core tip: Radial artery occlusion (RAO) is a rare but significant complication post-transradial percutaneous coronary intervention (PCI). We found that post-PCI Doppler flow signal-detected RAO incidence was not significantly different between Safeguard Radial and TR band compression devices. However, with the use of a novel air-inflation technique, we observed significantly lower incidence of RAO in all patients regardless radial compression device, in the short-term compared to current literature. Therefore, this novel air-inflation technique may offer a pragmatic and effective solution in reducing RAO incidence.

Voon V, Ayyaz Ul Haq M, Cahill C, Mannix K, Ahern C, Hennessy T, Arnous S, Kiernan T. Randomized study comparing incidence of radial artery occlusion post-percutaneous coronary intervention between two conventional compression devices using a novel air-inflation technique. *World J Cardiol* 2017; 9(11): 807-812 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i11/807.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i11.807

INTRODUCTION

Radial artery occlusion (RAO) is an increasingly recognized and significant vascular complication among those observed post-hemostatic compression device application for transradial percutaneous coronary intervention (PCI), the recommended access route in current guidelines[1]. As a consequence of RAO, ipsilateral limb transradial access may be rendered unusable for future procedures. This may be particularly crucial in post-PCI patients, a cohort at higher risk of requiring further coronary angiography, conduit for coronary artery bypass surgery or arterio-venous fistula formation for hemodialysis. Furthermore, ipsilateral ulnar artery access may be unusable due to ischemic limb risk on arterial cannulation.

Several studies have reported rates of RAO from 1%-30%[2-9]. These figures reflect the complex pathophysiology involved in RAO, particularly impaired vascular remodeling and thrombo-inflammatory alterations post-arterial injury. In addition, reports to date have been confounded by multiple external factors. These factors include heterogeneity of study designs, targeted patient populations, parameters for assessing RAO, anticoagulation as well as compression devices and techniques[10].

While several compression bands and techniques tested have demonstrated a modest reduction in RAO, a more pragmatic and effective approach remains to be defined[11]. Therefore, we aimed to prospectively compare incidence of RAO between two conventional hemostatic compression devices (Safeguard Radial and TR band) using a pragmatic and novel air-inflation technique, in patients post-transradial PCI.

MATERIALS AND METHODS

Ethics approval was obtained from University Hospital Limerick Ethics committee for our study, which conformed to the principles of the Helsinki Declaration. A total of 107 consecutive patients who had undergone transradial percutaneous coronary intervention at University Hospital Limerick, were screened and eligible patients were recruited into the study. Patients gave written informed consent prior to PCI and were prospectively randomized to either Safeguard Radial or TR band compression device *via* a pre-specified 1:1 automated randomization. Exclusion criteria were patients less than 18 years old, pregnancy, inability to consent, inability to attend follow-up clinic and difficult radial access requiring femoral access. Patient demographics and angiographic profiles were collected. All patients received dual anti-platelet therapy prior to PCI. Radial artery procedural preparation and management as well as RAO assessment are described below.

Radial artery cannulation

After sterile preparation, 1% lidocaine was injected at puncture site. The radial artery was punctured at the anterior wall with a 21-gauge arterial needle through which a 0.018-inch straight floppy tip guidewire (40-cm length) was advanced upon appearance of pulsatile flow. Following this, the needle was withdrawn and a hydrophilic 6F introducer sheath (11-cm length) with dilator length of 16 cm (Prelude, Merit Medical

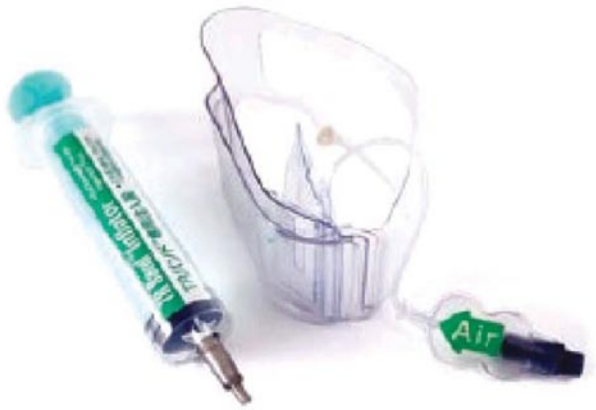

Figure 1 TR band compression device.

Systems) was inserted over the guidewire into the radial artery. Subsequently, the wire and dilator were removed. According to operator preference, a "radial cocktail" consisting of intra-arterial 100-200 mcg nitroglycerin, 250 mcg verapamil and heparin 2000-4000 IU, was given. All patients had total procedural heparin 70-100 IU/kg given as part of the PCI procedure.

Radial sheath removal and hemostatic compression technique

Patients were randomized to either TR band (Terumo Interventional Systems) or Safeguard Radial (Merit Medical) hemostatic compression device groups (Figures 1 and 2). Immediately post-PCI, the radial sheaths were pulled out 4-5 cm and chosen hemostatic compression device band was placed around wrist, with the transparent bladder immediately over the puncture site. We utilized a novel and pragmatic air-inflation technique that involved initial syringe-guided inflation of 2-5 mL of air into device transparent bladder *via* a cuff-valve system, with careful simultaneous removal of sheath. Continued inflation up to 5-10 mL of air was done to stop bleeding after complete removal of sheath. This was followed by immediate release of air, using similar syringe until bleeding/oozing point, at which an additional 2 mL of air was inflated into device bladder. This is contrary to current non-personalized air-inflation techniques utilizing standard 15 mL and 7 mL of air in TR band and Safeguard respectively, as per manufacturer's instructions. Subsequent gradual down-titration of air (1 mL of air removed every 30 min) was performed by nursing staff until completion of hemostasis.

Activated clotting time measurement

Activated clotting time (ACT) is the routine method of choice for monitoring heparin therapy during PCI. At the end of PCI, for all patients, 5 mL of fresh arterial blood sample was obtained in a 5 mL syringe after initially discarding 10 mL of blood from radial sheath prior to sheath removal. The fresh blood was immediately measured for ACT, by using a disposable single-use point-of-care assay. The assay consists of a cuvette containing manufacturer reagents and is measured by the accompanying battery-operated, hand-held device Hemochron Jr Signature + Whole Blood Microcoagulation System (International Technidyne) as per manufacturer's instructions.

RAO assessment

The handheld ultrasonic Doppler signal flow detector 2 MHz (FD1, Huntleigh, Sonicaid) probe was applied above the puncture site of radial artery of resting and extended forearm. RAO was defined as absence of Doppler signal flow. This was performed at 24 h and 6 wk post-PCI by operators blinded to randomization process.

Outcome measures

Primary endpoint was RAO at 24 h post-procedure and 6 wk follow-up. Secondary endpoints were bleeding requiring transfusion/surgical intervention, hematoma and pain/numbness at radial access site.

Statistical analysis

As a pilot study evaluating this technique, exploratory analyses was performed. Continuous normal data were expressed as mean ± SD. Continuous non-normal and categorical variables were expressed as mean (25^{th}, 75^{th} percentile) or frequencies (and percentages). Accordingly, between-group comparisons were compared using unpaired t-testing, Mann-Whitney rank sum test or Pearson chi-square tests. All patients with missing data were excluded from analyses. All analyses were performed using SPSS version 18 statistical software (SPSS Inc, Chicago, IL, United states). $P < 0.05$ was considered significant (two-tailed significance).

RESULTS

Baseline demographics of patient cohort are presented in Table 1. A total 84 patients were included for analyses after excluding patients who were not eligible ($n = 5$)/refused ($n = 2$), had missing data ($n = 16$). No significant differences were observed between-groups in terms of demographics or procedural profiles (Table 2). Approximately 60% of patients presented with an acute coronary syndrome. All patients had 6F radial sheaths inserted. Despite no significant between-group differences in post-procedural outcomes measures, both Safeguard Radial and TR band groups demonstrated very low incidence of RAO at 24 h (2% *vs* 0%) and 6 wk (0%, both) (Table 3). No significant

Figure 2 Safeguard Radial compression device.

Table 1 Clinical and angiographic profiles of Safeguard Radial *vs* TR band groups at baseline-total patient cohort

Variables	Safeguard radial, *n* = 42	TR band, *n* = 42	*P* value
Age, years	63.8 ± 10.9	66.8 ± 10.8	0.21
Gender, male/female ratio	31/11	37/5	0.16
BMI, kg/m^2	29.2 ± 3.9	29.0 ± 5.7	0.88
Diabetes	4 (10%)	8 (19%)	0.22
CKD	1 (2%)	2 (5%)	0.56
PAD	0%	1 (2%)	0.32
Indication			
Elective	18	16	0.88
UA	6	8	0.9
NSTEMI	13	8	0.7
STEMI	5	10	0.6

BMI: Body mass index; CKD: Chronic kidney disease; PAD: Peripheral arterial disease; UA: Unstable angina; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

differences in secondary outcome measures were observed.

DISCUSSION

This study has demonstrated no significant difference in incidence of short-term RAO between Safeguard and TR band devices. However, we have for the first time demonstrated significantly lower incidence of RAO at 24 h and at 6 wk post-PCI compared to current literature, regardless of type of conventional hemostatic compression device using the novel air-inflation technique. Among the few studies that have reported short-term RAO, some have observed RAO incidence as high as 9.2% at discharge[9]. Pancholy and colleagues reported RAO incidence of 4.4% at 24 h and 3.2% at 30 d using TR band in a cohort using 5F radial sheaths[8]. Dai *et al*[11] demonstrated that in post-transradial PCI patients, incidence of RAO was at least 11% at 24 h and 10% at 30 d. The study showed that air titration based compression strategy using TR band was superior to non-air titration strategies. However, the study utilized a non-specific, non-personalized method using manufacturer's instructions.

In our experience, additional 2 mL of air above point of bleeding/oozing provides personalized and adequate temporary patent hemostasis without the need of conventional methods to monitor radial patency. This has been shown despite different surface area of compression bladder of both devices. This magnitude of air may provide sufficient compression on muscle, adipose tissue and artery although impact of higher magnitudes of air remains to be determined. This technique requires confirmation in future studies.

To further support this technique, our study involved a cohort presenting predominantly with acute coronary syndrome, a more prothrombotic state, compared to previous studies. Only 29.7% of transradial PCI-treated patients presented with acute coronary syndrome in a study by Rathore and colleagues[9]. The study demonstrated a higher incidence of RAO as aforementioned with manufacturer's technique of compression device air inflation. However, several techniques to measure RAO were used and only 50% of patients had hydrophilic radial sheaths compared to our study. Some may argue that lack of sheath hydrophilicity may account for such results.

Furthermore, sheath size has also been a regarded as a contributing factor to RAO. Larger diameter sheaths have been reported to have increase RAO

Table 2 Procedural profiles of Safeguard Radial *vs* TR band groups

Variables	Safeguard radial, *n* = 42	TR band, *n* = 42	*P* value
Pre-procedure			
IR verapamil, %	(86%)	(83%)	0.77
IR nitroglycerine, %	(31%)	(45%)	0.18
Procedural			
Heparin, IU	7778 ± 2704	7825 ± 2450	0.94
Number of target vessels treated with PCI			
1			
2	39	39	1
≥ 3	3	3	1
	0	0	1
Target vessels			
LM	1	0	0.98
LAD/Diagonal	19	22	0.87
LCx/OM	7	7	0.96
RCA	18	12	0.64
IM	0	2	0.77
VG	0	2	0.77
Fluoroscopy times, min	15.3 ± 8.4	15.0 ± 6.9	0.88
Post-procedure			
GP2B3A inhibitor, %	1 (2%)	0%	0.32
ACT (s)	197 ± 38	197 ± 47	0.97

IR: Intra-radial; LM: Left main artery; LAD: Left anterior descending artery; LCx: Left circumflex artery; OM: Obtuse marginal artery; RCA: Right coronary artery; IM: Intermediate artery; VG: Vein graft; GP2B3A: Glycoprotein 2B 3A receptor; ACT: Activated clotting time.

Table 3 Post-procedural outcomes in Safeguard Radial *vs* TR band groups

Variables	Safeguard radial, *n* = 42	TR band, *n* = 42	*P* value
Bleeding requiring blood transfusion/surgical intervention	0%	0%	1
Hematoma	7%	0%	0.07
Pain/numbness	2%	0%	0.32
Radial artery occlusion at 24 h	2%	0%	0.32
Radial artery occlusion at 6 wk	0%	0%	1

incidence[12-14]. This effect was not observed in our study which used 6F sheaths in all patients who required PCI. Despite that, further studies involving improved imaging modalities are required to more accurately characterize vessel to sheath ratio. This is because the higher prothrombotic effects due to possible oversized sheaths may be offset by heparin therapy that all patients received in our study.

Heparin itself has been shown to reduce incidence of RAO. The lack of procedural heparin is an independent predictor of RAO[9]. Rathore and colleagues demonstrated RAO incidence of 24.1% at 4-6 mo follow-up in those without heparin administration. The study showed that in 92% of patients who had transradial PCI with 6F sheaths, RAO incidence was 8.9% at discharge and 5.6% at follow-up in the TR band group, which demonstrated lesser RAO between compression devices compared. Lefvre *et al*[15] reported 30% RAO with 1000 IU of heparin. This requires further confirmation, particularly at different comparator doses. However, the results of our study again emphasize the impact of the novel air-inflation technique in reducing RAO beyond conventional anticoagulation.

Several limitations were observed during the study. Firstly, we observed a high prevalence of missing data due to procedures performed out-of hours. However, both groups were well matched in baseline demographics to negate group bias effects. Second, as with all exploratory studies, type Ⅰ error may contribute to the results. Despite our study demonstrating consistent results at discharge and follow-up, this requires further confirmation. Third, Allen's test was not routinely performed pre-PCI. However, conventional methods of assessment *via* plethysmography and oximetry have not yielded consistent results due to influence of collaterals from palmar arches and recanalization[6,16]. Lastly, a known confounding factor that was not measured but critical for vascular management, was increased vigilance using our personalized air-inflation strategy to reduce RAO.

In conclusion, Safeguard Radial and TR band did not demonstrate significant between-group differences in short-term RAO incidence. Lack of evidence of RAO in all post-PCI patients at 6 wk follow-up, regardless of radial compression device indicate advantage of

using the novel and pragmatic air-inflation technique. Further work is required to more accurately confirm these findings.

COMMENTS

Background

Radial artery occlusion is a rare but significant complication post-transradial percutaneous coronary intervention, which is increasing in its use, globally. Therefore, better radial artery compression techniques are required to reduce such complication.

Research frontiers

Conventional radial artery compression devices by varying air-inflation techniques have shown different results in reducing the incidence of radial artery occlusion post-percutaneous coronary intervention. These suggest that novel air-inflation techniques using such devices may yield better results in reducing incidence of radial artery occlusion.

Innovations and breakthroughs

The authors have shown a much lower short-term incidence of post-percutaneous coronary intervention radial artery occlusion, compared to current literature, using a novel and pragmatic air-inflation technique in two conventional radial compression devices, Safeguard Radial and TR band.

Applications

This pilot study's methods and results of this study could be used in a larger prospective study aiming to the impact of this novel air-inflation technique with two conventional radial compression devices in different settings of transradial percutaneous coronary intervention.

Terminology

Radial artery occlusion is a rare but significant complication of transradial percutaneous coronary intervention. Novel and pragmatic radial compression techniques are required to reduce the incidence of such complication.

Peer-review

This is an interesting manuscript about the comparison of post-percutaneous coronary intervention radial artery occlusion incidence between two conventional radial artery compression devices using a novel air-inflation technique, Safeguard Radial and TR band.

REFERENCES

1 **Kotowycz MA**, Dzavík V. Radial artery patency after transradial catheterization. *Circ Cardiovasc Interv* 2012; **5**: 127-133 [PMID: 22338002 DOI: 10.1161/CIRCINTERVENTIONS.111.965871]

2 **Kiemeneij F**, Laarman GJ, Odekerken D, Slagboom T, van der Wieken R. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the access study. *J Am Coll Cardiol* 1997; **29**: 1269-1275 [PMID: 9137223]

3 **Stella PR**, Kiemeneij F, Laarman GJ, Odekerken D, Slagboom T, van der Wieken R. Incidence and outcome of radial artery occlusion following transradial artery coronary angioplasty. *Cathet Cardiovasc Diagn* 1997; **40**: 156-158 [PMID: 9047055]

4 **Nagai S**, Abe S, Sato T, Hozawa K, Yuki K, Hanashima K, Tomoike H. Ultrasonic assessment of vascular complications in coronary angiography and angioplasty after transradial approach. *Am J Cardiol* 1999; **83**: 180-186 [PMID: 10073818]

5 **Zhou YJ**, Zhao YX, Cao Z, Fu XH, Nie B, Liu YY, Guo YH, Cheng WJ, Jia DA. [Incidence and risk factors of acute radial artery occlusion following transradial percutaneous coronary intervention]. *Zhonghua Yi Xue Za Zhi* 2007; **87**: 1531-1534 [PMID: 17785103]

6 **Sanmartin M**, Gomez M, Rumoroso JR, Sadaba M, Martinez M, Baz JA, Iniguez A. Interruption of blood flow during compression and radial artery occlusion after transradial catheterization. *Catheter Cardiovasc Interv* 2007; **70**: 185-189 [PMID: 17203470 DOI: 10.1002/ccd.21058]

7 **Zankl AR**, Andrassy M, Volz C, Ivandic B, Krumsdorf U, Katus HA, Blessing E. Radial artery thrombosis following transradial coronary angiography: incidence and rationale for treatment of symptomatic patients with low-molecular-weight heparins. *Clin Res Cardiol* 2010; **99**: 841-847 [PMID: 20625752 DOI: 10.1007/s00392-010-0197-8]

8 **Pancholy S**, Coppola J, Patel T, Roke-Thomas M. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional versus patency documented hemostasis after transradial catheterization. *Catheter Cardiovasc Interv* 2008; **72**: 335-340 [PMID: 18726956 DOI: 10.1002/ccd.21639]

9 **Rathore S**, Stables RH, Pauriah M, Hakeem A, Mills JD, Palmer ND, Perry RA, Morris JL. A randomized comparison of TR band and radistop hemostatic compression devices after transradial coronary intervention. *Catheter Cardiovasc Interv* 2010; **76**: 660-667 [PMID: 20506228 DOI: 10.1002/ccd.22615]

10 **Wagener JF**, Rao SV. Radial artery occlusion after transradial approach to cardiac catheterization. *Curr Atheroscler Rep* 2015; **17**: 489 [PMID: 25651786 DOI: 10.1007/s11883-015-0489-6]

11 **Dai N**, Xu DC, Hou L, Peng WH, Wei YD, Xu YW. A comparison of 2 devices for radial artery hemostasis after transradial coronary intervention. *J Cardiovasc Nurs* 2015; **30**: 192-196 [PMID: 24496325 DOI: 10.1097/JCN.0000000000000115]

12 **Dahm JB**, Vogelgesang D, Hummel A, Staudt A, Völzke H, Felix SB. A randomized trial of 5 vs. 6 French transradial percutaneous coronary interventions. *Catheter Cardiovasc Interv* 2002; **57**: 172-176 [PMID: 12357515 DOI: 10.1002/ccd.10321]

13 **Takeshita S**, Asano H, Hata T, Hibi K, Ikari Y, Kan Y, Katsuki T, Kawasaki T, Masutani M, Matsumura T, Premchand RK, Rao SP, Suzuki T, Takahashi A, Takeda R, Tanaka S, Yamazaki S, Yin WH, Yoshimachi F, Saito S; NAUSICA Trial Investigators. Comparison of frequency of radial artery occlusion after 4Fr versus 6Fr transradial coronary intervention (from the Novel Angioplasty USIng Coronary Accessor Trial). *Am J Cardiol* 2014; **113**: 1986-1989 [PMID: 24786357 DOI: 10.1016/j.amjcard.2014.03.040]

14 **Wu SS**, Galani RJ, Bahro A, Moore JA, Burket MW, Cooper CJ. 8 french transradial coronary interventions: clinical outcome and late effects on the radial artery and hand function. *J Invasive Cardiol* 2000; **12**: 605-609 [PMID: 11103026]

15 **Lefevre T**, Thebault B, Spaulding C, Funck F, Chaveau M, Guillard N, Guillard N, Chalet Y, Bellorini M, Guerin F. Radial artery patency after percutaneous left radial artery approach for coronary angiography. The role of heparin. *Eur Heart J* 1995; **16**: 293

16 **Kwan TW**, Ratcliffe JA, Chaudhry M, Huang Y, Wong S, Zhou X, Pancholy S, Patel T. Transulnar catheterization in patients with ipsilateral radial artery occlusion. *Catheter Cardiovasc Interv* 2013; **82**: E849-E855 [PMID: 23008162 DOI: 10.1002/ccd.24662]

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