THE COMPLEX RELATIONSHIP BETWEEN CAFFEINE AND ARRHYTHMIAS

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ABSTRACT

Introduction*: The relationship between caffeine and arrhythmias is controversial. Several studies have been performed to evaluate the potential pro-arrhythmic effects of caffeine leading to opposite conclusion. The aim of the present commentary was to evaluate the relationship between arrhythmias and caffeine.*

Materials and methods*: The present review analyzes pre-clinical and clinical studies evaluating the relationship between caffeine and arrhythmias, with a look at the effects of highly caffeinated beverages.*

Results*: A difference has been reported between the effect of daily coffee consumption and high acute caffeine intake as happened in energy drink ingestion. Caffeine might not be arrhythmogenic except at very high doses and in subjects with high sensitivity, however the mix of caffeine and other substances such as guaranine or taurine could enhance the trigger of arrhythmias.*

Conclusions*: In conclusion caffeine at regular dose is not associated with arrhythmias. On contrary intake of high quantity of caffeine (i.e. highly caffeinated beverages) could trigger the development of arrhythmias.*

Key words*: caffeine, coffee, energy drinks, arrhythmias.*

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Introduction

The relationship between caffeine and arrhythmias is controversial. Several studies have been performed to evaluate the potential pro-arrhythmic effects of caffeine leading to opposite conclusion. The major bias is related to the source of caffeine in real-life. Many food and beverages contain caffeine and the source can influence absorption and bio-availability of the very active substances[1,2,3,4].

Coffee is among the most commonly consumed beverages in Western Countries and is the main source of caffeine intake among adults[1,2]. On the contrary the intake of caffeine in young people is mainly related to beverages like cola soda and energy drinks (EDs)[3,4,5].

The biological impact of coffee may be substantial and is not limited to the effects of caffeine (Table 1). Regular coffee consumption has been associated with a lower risk of cardiovascular risk factors such as of type 2 diabetes mellitus, obesity and depression[1]. Furthermore, large observational studies have found that habitual coffee drinkers have lower rates of cardiovascular and all-cause mortality[6].

The estimated caffeine from coffee consumption in Mediterranean countries is about 198 mg/day per person, similar to that reported in USA, 210 mg/day[3]. Ingestion of a single cup of espresso coffee provides a dose of 0.4-2.5 mg/kg of caffeine (calculated as 80-90 mg/cup of espresso)[4]. The variability in caffeine content in coffee is influenced by several

factors: the quality of coffee beans (Arabica or Robusta), the roasting method, the modality of preparation (percolation, espresso, instant coffee) and length of brewing time. From chemistry, a longer extraction time gives coffee more caffeine than a shorter one (for e.g. an espresso vs an american coffee)[4].

	Acute effects	Chronic effects
Blood pressure	↑	= or ↓
Arterial Stiffness	↑	=
Insulin sensitivity	↓	n.a.
Diabetes type 2	n.a.	↓
Heart rate	↑	= or ↓

Table 1: Most common effects of caffeine on cardiovascular system.

The content of caffeine in food and beverages ranges from 4 to 180 mg/150 ml for coffee to 24 to 50 mg/150 ml for tea, 15 to 29 mg/180 ml for cola, 2 to 7 mg/150 ml for cocoa and 1 to 36 mg/28 mg for chocolate, more than 160 mg/355 ml for energy drinks[3,4]. Compared to energy drinks, coffee is a poor source of caffeine (Table 2).

	Dose (ml)	Caffeine mean (mg)
Espresso coffe (capsule)	30	60 (range 40 - 90)
Espresso Coffee (Moka)	60	120 (range 90-150)
American Coffee	240	135 (range 102 - 200)
Instant Coffee	240	97 (range 27 - 173)
Decaffeinated Coffee	240	4 (range da 3 - 9)
Espresso Coffee decaffeinated	30	4 (range 0-4)
Tea	240	53 (range da 40 a 120)
Coka-Cola® (regular or sugar free)	355	Range 35 - 47
Pepsi® (regular or sugar free))	355	Range 36 - 38
Monster Energy®	475	160
Red Bull®	245	80
Monster Energy®	475	160
5-Hour Energy®	60	215

Table 2: Caffeine in different beverages: [modified from Mattioli AV, 2007).

Coffee, additionally to caffeine, contains many different substances, including high levels of phenolic antioxidants consisting principally of chlorogenic acids (CGAs). The total content of CGA in a ''regular'' cup of coffee (200mL) varies between 70 and 350mg[7]. Therefore, if coffee is consumed throughout the day, it may provide up to two thirds of total daily dietary antioxidants[8,9]. While phenolic metabolites of CGA have been studied for potential bioefficacy, controversy remains as to how efficient those compounds actually are in reducing the risk of chronic disease[10,11].

Lifestyle, nutrition and physical activity is a cornerstone in prevention of cardiovascular disease. Core components of a healthy diet include limiting intakes of saturated and trans fats, carbohydrate, alcohol, and sodium and increasing intakes of fruit, vegetables, (rich in antioxidants) and dietary fibers. The Mediterranean Diet meets these healthy diet requirements. The very recent Mediterranean Diet pyramid included at the basis the physical activity as well as moderate consumption of both coffee and wine[12,13].

The recent Covid-19 pandemic and the forced collective quarantine of populations have had a profound impact on lifestyle, food habits and have affected the global coffee sector, including production, consumption and international trade[14,15].

In the short-term, out-of-home consumption is decreasing significantly as an effect of a full or partial lockdown in several Countries. Offices, coffee shops and restaurants remain closed in order to reduce the spread of the CoV-19/SARS-CoV-2.

On the other hand, retail- and supermarket-level data suggest that panic buying and stockpiling has led to increased consumer demand in some countries. However, this is unlikely to have a sustained effect on consumption. Following an initial spike in demand, there will be proportionally less demand in the coming weeks and months as consumers draw down stocks kept at home[16].

A recent paper analyzed the changes in food choice following restrictive measures due to Covid-19 and found an increase of 15.2% in coffee purchase[17].

Several experimental and clinical studies have sought to determine the impact of caffeine on cardiac arrhythmias.

Our search strategy was designed to inform this Review relating to effects of caffeine on arrhythmias. We searched MEDLINE, Scopus and Web of Science. In brief, we used a combination of terms relating to caffeine (eg, "caffeine" and "coffee") and arrhythmias (eg, "ventricular arrhythmias" and "atrial fibrillation") and "energy drinks" and "highly caffeinated beverages". For studies to be included in this Review, they had to report on primary research, be published in peer-reviewed journals, be written in English and include data on the prevalence of arrhythmias.

The present rapid review briefly analyzes the effects of caffeine on arrhythmias with a section specifically related to energy drinks, highly caffeinated beverages.

Main body

Caffeine as a trigger for arrhythmias

Caffeine-rich beverages have been traditionally considered the main nutritional trigger involved in symptoms like palpitations and heartbeat irregularities in clinical practice. However, these symptoms might be the signal of potentially dangerous arrhythmic events and need specific evaluation of heart. The 25% of patients presenting with palpitations thought that coffee was the triggering-factor[18].

Isolated case reports have suggested a direct association between caffeine consumption and sudden death, presumably mediated by severe ventricular arrhythmias[19] (Table 3).

Low dose	High dose
Sinus bradicardia	Sinus arrhythmias
Sinus arrhythmias	Atrial ectopics
Sinus arrest	Atrial tachycardia
Atrial ectopics	Wandering of pacemaker
Wandering of pacemaker	Ventricular premature contractions (unifocal 64%, multifocal 32% versus control)
Ventricular premature contractions	Ventricular tachycardia

Table 3: Most common effects of low dose and high dose of caffeine in pre-clinical studies.

However, studies carried to evaluate the effect of caffeine ingestion on ECG and arrhythmias concluded that although caffeine is probably not arrhythmogenic in normal subjects, moderate ingestion does produce a small but statistically significant prolongation of signal-averaged QRS complexes. Further prolongation caused by excessive caffeine intake may be a factor in the genesis of arrhythmias associated with caffeine toxicity due to high dosage ingestion[20-22]. All these studies confirm that there is no physiopathological basis supporting a link between caffeine and arrhythmias at regular daily dose.

The metanalysis carried on by Zucchinali et al evaluated the risk for occurrence of Ventricular premature beats in 24 h attributed to caffeine in 7 clinical studies[23].

Sensitivity analysis for study design, caffeine dose and subject condition (healthy and unhealthy status) was performed and no major differences were observed. Authors observed increased heterogeneity in subgroups. The highest caffeine dose was 450 mg (roughly equivalent to four to five cups of regular coffee) and the lowest dose was 175 mg (roughly equivalent to a single dose). These observations support the hypothesis that caffeine doses regularly consumed in a daily basis are not associated with increased risk of arrhythmia. There is no scientific data that supports a clinical recommendation to decrease or avoid caffeine consumption in patients with palpitations and without cardiac specific disease. Prospective clinical trials did not demonstrate an increase in clinically significant ventricular or supraventricular arrhythmias, even after exposure to high doses of caffeine[1].

In addition, large epidemiologic studies did not demonstrate a significant association of caffeine intake with increased rates of arrhythmias, specifically Atrial fibrillation (AF).

AF is the most common arrhythmias in adult population, but, despite the large number of studies available, triggers have not been completely identified.

The Danish Diet, Cancer and Healthy, a wide prospective study, suggested that caffeine consumption was not associated with hospitalizations for AF in a population with high caffeine intake (24) More recently, the long term follow-up analysis of the Danish Cohort (median follow-up of 13.5 years) found that compared with no intake, coffee consumption was inversely associated with AF incidence, with multivariable-adjusted hazard ratios of 0.93 (95% CI 0.74-1.15) for more than none to <1 cup/day, 0.88 (95% CI 0.71-1.10) for 1 cup/day, 0.86 (95% CI 0.71-1.04) for 2–3 cups/day, 0.84 (95% CI 0.69-1.02) for 4-5 cups/day, 0.79 (95% CI 0.64-0.98) for 6-7 cups/day and 0.79 (95% CI 0.63-1.00) for >7 cups/day (p-linear trend = 0.02). Leading to the conclusion that higher levels of coffee consumption were associated with a lower rate of incident AF[25].

In a population-based study amongst men coffee consumption was not associated with hospitalization for AF[26]. The Cardiovascular Health Study included a total of 1416 individuals and found no evidence that the frequency of Caffeinated beverages (habitual coffee, tea, or chocolate) consumption was associated with cardiac ectopy[27].

A similar conclusion was reported in the Women's Health Study, where caffeine consumption was not associated with an increased risk of incident AF in healthy, middle-aged women. Women with highest caffeine consumption had a similar risk of developing AF during follow-up compared with women with lowest caffeine consumption.

Interestingly, women in the third quintile of caffeine consumption had a lower risk of incident AF (hazard ratio: 0.78; 95% CI: 0.64, 0.95), suggesting that the consumption of small to moderate amounts of caffeine might even be beneficial[28].

This is an important observation due to the known differences among women response to lifestyle changes[29,30].

Several meta-analyses showed no overall association between caffeine intake and AF risk. (31,32)

Interestingly, Cheng and coworkers showed that the risk of developing AF decreases by 6% for each increase of habitual intake of 300 mg of coffee, leading to consider that usual intake of caffeine may even be protective against arrhythmic outcomes. They suggested that habitual caffeine consumption might reduce AF risk by its antifibrosis effect[30]. [31,32,33]. Caffeine reduced hepatic fibrosis and inhibited liver fibrosis by interfering with transforming growth factor b signaling[34].

Although there are few studies that evaluated the antifibrosis effect of caffeine on the heart, it is possible that caffeine also prevent cardiac fibrosis[35,36]. At last, the protective effect of caffeine might be related to co-occurring phytochemicals because caffeine is normally consumed in the form of plant-derived products and extracts that invariably contain other potentially bioactive phytochemicals[37,38].

The meta-analysis performed by Cheng found that low caffeine intake but not moderate and high intakes was associated with a reduced risk of AF[31]. Caffeine exposure was not associated with an increased risk of AF (OR 0.92, 95% CI 0.82 to 1.04, I2=72%). to 0.94; I2=39%). Authors concluded that low-dose caffeine may have a protective effect[31].

A recent analysis from the Malmö Diet and Cancer Study performed on 112 metabolites found that caffeine and acisoga were also associated with an increased risk (HR, 1.17; 95% CI, 1.06-1.28 and 1.08; 95% CI, 1.00-1.18, respectively)[39].

Authors underlined that the finding of caffeine being associated with new-onset AF was surprising, because caffeine exposure has not been shown to increase the risk of AF in a systematic review of >100 000 individuals[32].

However, the potential association between plasma caffeine levels and AF was not linear. Caffeine quintile 5 displayed a significantly higher risk for AF compared with quintile 1, but other associations were not significant[39].

A possible explanation is that there are numerous factors influencing caffeine intake, absorption, metabolism, and physiologic and functional effects, which all could affect caffeine plasma levels, such as age, sex, hormonal status, diet, smoking, exposure to drugs, and genetic background[39]. These recent data need further evaluation.

Energy drinks and arrhythmias

The effect of daily coffee consumption is not comparable with high acute caffeine intake as happened in energy drink ingestion. Caffeine might not be arrhythmogenic except at very high doses and in subjects with high sensitivity[40-43]. Caffeine toxicity could induce different arrhythmias: case report referred about supraventricular tachycardia, atrial fibrillation and ventricular fibrillation. In many cases it has been suggest that high ingestion of energy drinks associated or not with alcohol could act as trigger of arrhythmias[44,45]).

Caffeine is a widely used energetic substance and many papers suggested great effects during endurance activities, leading to an increasing consumption of caffeinated beverages in non-professional athletes and young subjects.

A meta-analysis was performed to evaluate the ergogenic effect of caffeine on endurance time-trial performance. Caffeine showed a small but evident effect on endurance performance when taken in moderate doses (3-6 mg/kg) as well as an overall improvement following caffeine compared to placebo in mean power output ($3.03 \pm 3.07\%$; effect size $= 0.23 \pm 0.15$) and time-trial completion time ($2.22 \pm 2.59\%$; effect size $= 0.41 \pm 0.2$). However, differences in responses to caffeine ingestion have been shown[46].

Consumption of energy drinks by both recreational and competitive athletes has increased dramatically in recent years, for improving physical and mental performance. The reasons why these drinks are very diffuse within young people is probably mainly due to marketing campaign identifying it as safe and able to improve the physical and mental performance[47,48]. However, scientific literature shows contradictions about the capacity of energy drinks to enhance psychophysical results[49, 50].

Currently, there is not a common formula of commercial energy drinks. To date, there exists an abundance and variety of EDs on the market, with >200 brands in the United States alone[51]. However, only a few dominate the market, and there is not much difference in caffeine and sugar content when comparing the market leaders. They included many different substances, i.e. methylxanthines, taurine, creatine, carnitine, B vitamins, maltodextrin, inositol, and glucuronolactone; there are also herbs such as guarana (containing caffeine), ginseng and ginkgo biloba[52-55].

The guarana plant and berry has one of the naturally highest levels of caffeine and there are also traces of theophylline and theobromine. In addition

caffeine and a possible combination of caffeine and taurine may negatively influence hemodynamic variables, with increase of blood pressure and heart rate and increase in stroke volume[56].

About half of college student "ED users" consumed EDs while studying or working on a major project[57]. Specifically, 51% of college students consume at least one energy drink per month and almost a third of students between grades 8 and 12 drink them[57].

More than 70% of ED users were 18 to 22 years old and were mostly males (51.8). Working students are more likely to drink EDs (OR 1.5). The most often used combinations were ED containing alcohol (65.6%) and ginseng-coffee beverages (71.8%)[58].

Today many case report underline the role of energy drinks as trigger for arrhythmias[59,60]. In addition 8 case reports found an association between large intakes of EDs and myocardial ischemia, with no additional triggers in the majority of cases[61]. Among 855 documented "energy drink" exposures, the Texas poison centers determined outcome severity and revealed 291 with no/minimal effects, 417 judged nontoxic or minor/not followed, 64 moderate and 4 major effects, and no deaths. Serious complications included 2 seizures and 1 episode of ventricular tachycardia[62].

Directions for future research

With the increasing popularity of highly caffeinated beverage in the young population physicians should be aware of the arrhythmogenic potential associated with consumption and the Food Regulatory Agencies need to consider new regulation of these products but product specificity is needed to evaluate safety[3, 42]. A randomized trial evaluating health damages of energy drinks in young people is needed.

In conclusion caffeine at regular dose is not assoiated with arrhythmias. On contrary intake of high quantity of caffeine (i.e. highly caffeinated beverages) could trigger the development of arrhythmias. Coffee is a very diffuse source of caffeine and in several population studies shows to act positively on cardiovascular risk factors. The main important factor seems to be the dose of caffeine, however we cannot exclude that preparation and interaction with other food contribute to the final effect on the cardiovascular system.

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