

STATE-OF-THE-ART REVIEW

Caffeine and Arrhythmias

Time to Grind the Data



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ABSTRACT

The interaction between arrhythmia episodes and certain lifestyle factors such as obesity and alcohol is well established. There is significant public and professional interest in the role of caffeinated beverages such as coffee, tea, and energy drinks in cardiovascular health. However, many widely held beliefs are not supported by evidence. This study provides a comprehensive review of the impact of caffeinated beverages on cardiac rhythm. (J Am Coll Cardiol EP 2018;4:425-32)
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The importance of lifestyle-related risk factors is increasingly recognized in the management of atrial fibrillation (1), and there is considerable public interest in the impact of coffee, tea, and energy drinks (EDs) in arrhythmogenesis. The latest American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for management of patients with atrial fibrillation (2) and ventricular arrhythmia (VA) (3) address the role of alcohol as a potential trigger for arrhythmias, however, they do not refer to caffeinated beverages, which are equally ubiquitous in Western culture. Coffee is a stimulant and is the most common form of cognitive enhancement (4). It has been assumed that, because of the effects of caffeine on enhancing the mind and heart rate, it may contribute to arrhythmia. This public perception is often based on anecdotal experience; however, the perception extends to the medical community, with more than 80% of U.S. physicians recommending abstinence or reduction in caffeine intake for patients with palpitations or documented

arrhythmias (5). Extensive research over the past decade suggests that many widely held beliefs regarding caffeine may not be evidence-based. This study performed a detailed review of published reports to determine the interactions between coffee, tea, and EDs and rhythm disorders.

METHODS

We performed a comprehensive search of Medline, EMBASE, Web of Science, and PubMed, focusing on human and animal studies published in English that examined the effects of caffeine on both atrial arrhythmias and VAs. Prospective, retrospective, observational, and interventional studies were all included in the search. Key search terms were “caffeine,” “coffee,” “tea,” and “energy drinks” in combination with “arrhythmias,” “atrial fibrillation,” “sudden death,” “ectopy,” and “ventricular arrhythmias.” Conference abstracts were excluded. No restriction was placed on the year of study publication.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation and/or flutter

ED = energy drink

HR = Hazard ratio

OR = odds ratio

SCD = sudden cardiac death

SVT = supraventricular tachycardia

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

CAFFEINE PHARMACOLOGY. Caffeine is the primary constituent in coffee (1 cup of coffee contains ~95 mg of caffeine) and is also found in tea, soft drinks, and EDs (Table 1). It acts as a methylxanthine alkaloid and central nervous system stimulant. Caffeine's half-life is 5.7 h, with nearly 100% bioavailability, and maximum concentrations are reached within 1 h of consumption (6).

Caffeine has a range of effects on sympathetic activation, intracellular calcium trafficking, adenosine receptors, and is an antioxidant. Caffeine increases the sinus rate by sympathomimetic effects mediated by phosphodiesterase inhibition and a rise in cytosolic calcium concentration by blocking calcium reuptake into the sarcoplasmic reticulum (Central Illustration) (7). An increase in intracellular calcium has the potential to induce atrial arrhythmia by enhancing automaticity of atrial pacemaker cells and after depolarization-induced triggered activity (8). A dose of 250 mg of caffeine (3 cups of coffee) acutely increases norepinephrine and epinephrine by 75% and 207%, respectively (9). At very high doses, caffeine may be proarrhythmic. In a murine study, the administration of 15 mg/kg per min caffeine resulted in sympathetic over-activation, with sinus tachycardia and ventricular ectopy culminating in ventricular fibrillation (VF) in all rats. Effects were partially reversed by administration of beta-blockers (10).

Proposed antiarrhythmic properties of caffeine may be mediated in part by nonselective inhibition of adenosine A₁ and A_{2A} receptors (11). Adenosine shortens atrial refractoriness and may trigger atrial fibrillation during acute administration (12). In addition, caffeine and the polyphenols found in coffee have antioxidant properties that may bind reactive oxidant species responsible for adverse atrial remodelling and atrial fibrillation (AF) (13). In fact, coffee has a higher level of antioxidant activity (292 to 948 min) than black tea (67 to 277 min) or herbal tea (6 to 78 min), on the basis of a cup serving (14). As such there are putative mechanisms by which caffeine may enhance or reduce arrhythmogenesis.

COFFEE AND ATRIAL ARRHYTHMIA. Experiment- and population-based studies have sought to determine the impact of caffeine on heart rhythm disorders. In a canine model, an intravenous injection of 1 to 5 mg/kg of caffeine unexpectedly reduced AF inducibility (15). In a human study, Lemery et al. (16) administered 5 mg/kg caffeine over 57 ± 13 min before electrophysiology study in patients with supraventricular tachycardia (SVT) and were unable to

demonstrate an effect on atrial or ventricular refractory periods or the inducibility of SVT. Dörmeyer et al. (17) also failed to show short-term effects on interatrial and intra-atrial conduction in humans. In a community-based cohort of 1,388 participants undergoing 24-h Holter monitoring, Dixit et al. (18) failed to demonstrate any association between higher caffeine intake and atrial or ventricular premature beats. Single high-dose caffeine (400 mg) did not affect electrocardiographic P-wave duration or P-wave dispersion in healthy volunteers (19). To date, clinical studies have failed to show deleterious effects of caffeine on atrial and ventricular electrophysiologic properties.

Population-based studies have consistently demonstrated a reduction in atrial fibrillation with increasing levels of caffeine ingestion. Incident AF events in 57,053 participants followed for 13.5 years were lower in habitual coffee drinkers at all levels of consumption (hazard ratio [HR]: 0.79 for 6 to 7 cups per day) (20). A meta-analysis of 6 prospective cohort studies with 228,465 participants similarly demonstrated an inverse relationship, with AF incidence decreasing by 6% for every 300 mg/day increment in regular caffeine intake (21). In a further meta-analysis of 115,993 patients, pooled results demonstrated a significant 13% reduction in incident AF risk (22). In a population-based study of 130,054 people, 3,137 subjects (2.4%) were hospitalized for arrhythmia over 17.6 years' follow-up. Caffeine intake was again inversely related to arrhythmia risk (HR highest vs. lowest quartile = 0.6; p = 0.03) (23).

Table 2 summarizes 11 major human studies (360,980 patients, 15,198 AF cases) examining the relationship between caffeinated beverages and atrial arrhythmia. One small case-control study with no adjustments for other confounders (24) reported coffee was detrimental, whereas 3 studies consistently demonstrated a benefit, and the remaining studies showed no significant interaction.

Nevertheless, one must exercise caution when extrapolating data from healthy volunteers and registries to individual patients. In all long-term observational studies, investigators followed regular long-term coffee drinkers; and caffeine tolerance may explain the lack of association with arrhythmias. Moreover, there may be individual differences in susceptibility to the effects of caffeine on electrophysiologic and autonomic factors that trigger arrhythmias in some people. Twenty-five percent of patients report coffee is an AF trigger (25), and those with a clear temporal association between coffee intake and documented AF episodes should accordingly be counseled to abstain.

COFFEE AND VENTRICULAR ARRHYTHMIA. Caffeine does not appear to increase the likelihood of VA. A study of 22 patients with a history of VAs who underwent electrophysiological study before and 1 h post-coffee (275 mg caffeine) ingestion demonstrated no significant difference in inducibility of VAs (26). In 5 placebo-controlled trials, caffeine in doses of up to 500 mg daily (~6 cups of coffee) did not experience an increase in the severity or frequency of VAs (27). In 50 consecutive patients with a history of malignant VAs receiving either coffee (containing 200 mg of caffeine) or a decaffeinated drink, there were no significant differences observed in ventricular ectopy or tachycardia, despite increases in serum catecholamine levels in the caffeinated group (28). A meta-analysis of 7 human studies found that caffeine consumption had no impact on incidence of ventricular ectopy (29).

Numerous randomized studies have explored the impact of caffeine intake and restriction on VAs. In a randomized study of 103 patients with post-myocardial infarction, regular caffeine (average: 353 mg/day) resulted in improved heart rate variability, increased parasympathetic activity, and no significant arrhythmias compared with controls (30). More recently, Zuchinali et al. (31) performed a double-blinded crossover trial in 51 patients with moderate-to-severe left ventricle dysfunction at high risk of VAs, consuming either 500 mg of caffeine or placebo. No significant differences were observed in supra-ventricular or ventricular ectopy, nor nonsustained ventricular tachycardia during continuous monitoring at rest and with exercise. In a randomized double-blind trial of caffeine restriction using decaffeinated coffee in patients with symptomatic ventricular premature beats, no significant changes were seen in palpitation scores or ectopic burden (32). Moreover, large epidemiological studies suggest that regular caffeine drinkers have lower cardiovascular (33) and all-cause mortality (34), with a potentially attenuated risk of coronary heart disease, heart failure, and stroke.

A summary of major human studies examining coffee consumption and VAs is presented in Table 3. Of 8 studies involving 232,717 patients, 6 studies demonstrated no association, including 3 well-designed prospective trials (28,29,35). Only 2 older studies (a case-control and a cross-sectional survey) demonstrated an association between coffee consumption and VAs at very high levels of coffee intake only (>10 cups per day [36] and >9 cups per day [37], respectively).

TEA. There are limited observational data suggesting that tea (particularly green tea) may be beneficial. Tea

TABLE 1 Caffeine Content of Common Commercially Available Caffeinated Beverages

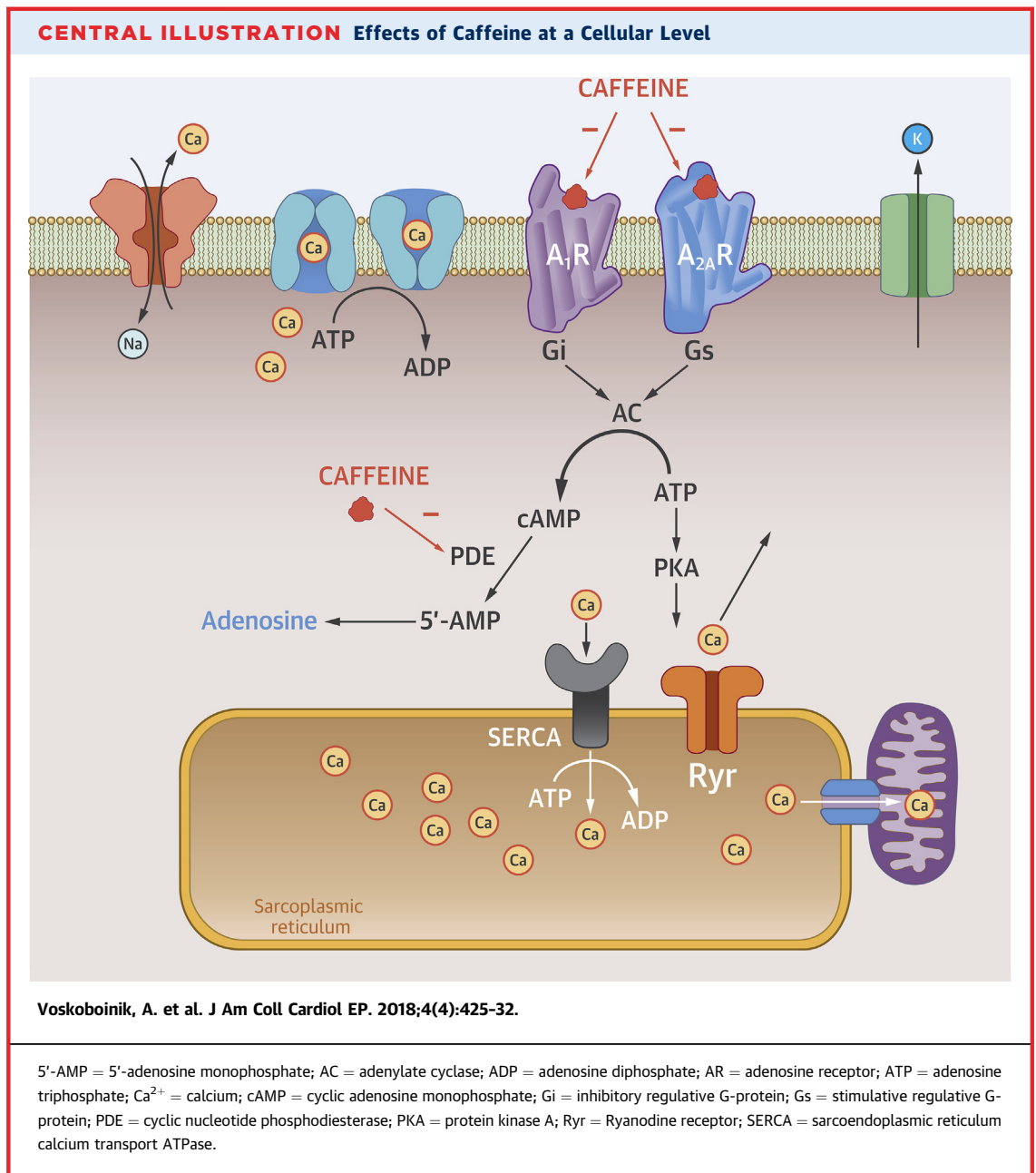
Beverage	Amount of Caffeine, mg	Volume, ml
Can of Coca Cola	32	375
Cup of Lipton green tea	35	150
Cup of Lipton black tea	55	150
Starbucks Café Latte - short	75	236
Espresso shot	106	25
Starbucks Café Latte - grande	150	473
Monster Energy drink	160	473
Wired X344 Energy drink	344	473
Fixx Energy drink	500	591

Coca Cola, Inc., Atlanta, Georgia; Fixx Beverage, LLC, Toms River, New Jersey; Lipton, Unilever Australia, Sydney, New South Wales, Australia; Monster, Hansen Natural Corporation, Corona, California; Starbucks, Tacoma, Washington; Wired, Wired Energy Drinks, Everett, Washington.

contains less caffeine than coffee and is rich in epigallocatechin gallate (EGCG), a catechin with antioxidant and anti-inflammatory properties. In a rabbit model, supplementation with EGCG was associated with prolongation of an atrial effective refractory period together with a reduction in AF inducibility and atrial fibrosis (38). In a case-control study of 801 subjects, green tea intake led to a significant reduction in paroxysmal and persistent AF (odds ratio [OR]: 0.35; 95% confidence interval [CI]: 0.25 to 0.48) (39).

Benefits of tea may also extend to reducing VAs. In a rat model, pre-treatment for 4 weeks of black tea consumption raised the threshold dose of aconitine for inducing VT ($p < 0.001$) and significantly reduced duration of VT and VF compared with those of controls (40). In humans, moderate tea consumption (up to 14 cups/week) was associated with a significant reduction in VAs (OR: 0.7; 95% CI: 0.6 to 0.9) in 3,882 patients following myocardial infarction (41). In a meta-analysis, consumption of 3 cups of tea per day significantly reduced the risk of cardiac death (relative risk 0.74; 95% CI: 0.63 to 0.86) (42).

ENERGY DRINKS. EDs often contain caffeine at significantly higher concentrations than coffee and tea, which have inhibitory effects on phosphodiesterases, promoting calcium release from intracellular stores and increasing myofilament sensitivity to calcium, mimicking the effects of adrenaline (43). Proarrhythmic effects may be augmented by other energy-boosting substances, such as guarana, sugar, ginseng, yohimbine, and ephedra (44), as well as by concurrent intake of alcohol and illicit drugs. Guarana, particularly, has a higher caffeine concentration than coffee and contains theophylline, which also has stimulant properties (45).



There have been increasing numbers of case reports relating to the temporal association between EDs and arrhythmias, including young patients without structural heart disease presenting with AF, SVT, VT, and VF shortly after consuming these beverages (46). Three quarters of patients who consumed 2 or more EDs/day reported palpitations within 24 h, compared with only 12% of occasional consumers ($p < 0.001$) (47).

In observational studies, EDs have been shown to lower heart rate variability (48) and prolong QTc interval (49). In patients with congenital long-QT

syndrome, dangerous QTc prolongation of ≥ 50 ms following ED consumption has been reported (50). There are isolated case reports of EDs unmasking long QT and Brugada syndromes (51). ED ingredients other than caffeine are responsible for the prolongation of QTc interval. In a randomized, double-blind crossover study in 18 healthy individuals who consumed either ED or caffeinated controls (each containing 320 mg of caffeine), significant QTc prolongation (0.44 ± 18.4 ms vs. -10.4 ± 14.8 ms, respectively; $p = 0.02$) was demonstrated in the ED group (52).

TABLE 2 Major Studies Examining Impact of Caffeinated Beverages on Atrial Arrhythmia

First Author (Ref. #), Year	Cases/Participants	% Males	Age, yrs	Follow-Up, yrs	Study Design	Key Findings
Mostofsky et al. (20), 2016	3,415/57,053	48	56.7 ± 4.4	13.5	Population-based cohort study	<ul style="list-style-type: none"> Higher coffee intake was associated with lower rate of incident AF (linear trend: p = 0.02). Compared to nondrinkers, OR: 0.86 (95% CI: 0.71 to 1.04) for 2-3 cups per day, and OR: 0.79 (95% CI: 0.64 to 0.98) for 6-7 cups per day
Dixit et al. (18), 2016	1,388	47	71.9 ± 5.0	NA	Observational study (24-h Holter)	<ul style="list-style-type: none"> No correlation between atrial ectopics/h and intake of coffee (p = 0.28) or tea (p = 0.57). No correlation between SVT runs and intake of coffee (p = 0.22) or tea (p = 0.90).
Liu et al. (39), 2016	401/801	56	63.0 ± 1.2	–	Case control	<ul style="list-style-type: none"> Green tea was protective against incident AF (multivariate OR: 0.349; 95% CI: 0.25 to 0.48) in a dose-dependent manner (p for trend = 0.001).
Larsson et al. (56), 2015	7,041/76,475	55	61.5	12	Population-based cohort study	<ul style="list-style-type: none"> No association between coffee consumption and risk of incident AF at all levels of consumption (multivariate RR: 0.98 for 2-3 cups/day; RR: 1.01 for ≥5 cups/day; p = 0.64 for trend).
Klatsky et al. (23), 2011	1,512/13,0054	44	–	17.6	Retrospective population cohort	<ul style="list-style-type: none"> Higher coffee intake was associated with lower rates of hospitalization for AF (HR: 0.81; 95% CI: 0.69 to 0.96 for ≥4 cups/day) and SVT (HR: 0.63; 95% CI: 0.41 to 0.98 for ≥4 cups/day)
Shen et al. (57), 2011	296/4,526	44	62 ± 10	4.0	Prospective cohort	<ul style="list-style-type: none"> No correlation between caffeine intake and risk of incident AF (for quartiles of intake for Q1 HR: 0.84; 95% CI: 0.62 to 1.15 vs. Q4 HR: 0.98; 95% CI: 0.7 to 1.39; p for trend = 0.84).
Conen et al. (58), 2010	945/33,638	0	53	14.4	Prospective cohort	<ul style="list-style-type: none"> U-shaped relationship with lowest risk of incident AF in third quintile of intake with median 285 mg/day (HR: 0.78; 95% CI: 0.64 to 0.95; p for quadratic trend = 0.03). None of the individual caffeine components (tea, coffee, cola, chocolate) was associated with incident AF.
Mukamal, et al. (59), 2009	163/1,369	70	59.8	6.9-9.9	Prospective cohort	<ul style="list-style-type: none"> In patients with previous myocardial infarction, coffee drinkers in the 4 higher categories of intake had ~30% lower risk of developing AF (HR for ≥1 cups/day: 0.65; 95% CI: 0.40 to 1.05).
Frost et al. (60), 2006	555/47,949	47	56	5.7	Prospective cohort	<ul style="list-style-type: none"> Compared with the lowest quintile, there was no association between caffeine intake and incident AF (lowest risk was third quintile, ~584 mg/day; HR: 0.85 (95% CI: 0.65 to 1.12).
Mattioli et al. (24), 2005	116/232	74	54 ± 7	–	Case control	<ul style="list-style-type: none"> High coffee intake, >3 cups/day, was associated with a lower rate of spontaneous cardioversion from AF (OR: 0.3; 95% CI: 0.11 to 0.49; p = 0.008).
Wilhelmsenet al. (61), 2001	754/7,495	100	47 ± 55	25.2	Population-based cohort study	<ul style="list-style-type: none"> Consumption of ≥5 cups/day was not associated with a higher risk of incident AF (OR: 1.09; 95% CI: 0.87 to 1.38), although moderate consumption reached borderline significance (OR: 1.24; 95% CI: 1.00 to 1.54).

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; NA = not applicable; OR = odds ratio; RR = relative risk; SVT = supraventricular tachycardia.

EDs may be responsible for a prothrombotic state, particularly relevant in patients with pre-existing structural heart disease or AF. Studies in healthy volunteers undergoing platelet function testing before and 60 min after ED consumption demonstrated a significant increase in platelet aggregation through arachidonic acid-induced activation (53) and endothelial dysfunction (54).

The concerns regarding the potential deleterious effects of EDs have been expressed in public policy. The U.S. Food and Drug Administration has forced

companies to include conventional nutritional fact panels with exact caffeine concentrations, following the reclassification of EDs as “beverages” rather than “dietary supplements” in an attempt to improve consumer safety. The International Society of Sports Nutrition recommends that patients with pre-existing cardiovascular conditions who are taking medications that may be affected by caffeine and other stimulants refrain from use of EDs, and they warn that more than 1 ED/day, even in healthy individuals, may be harmful (55).

TABLE 3 Major Studies Examining Impact of Caffeinated Beverages on Ventricular Arrhythmia

First Author (Ref. #), Year	Cases/Participants	% of Males	Age, yrs	Follow-Up, yrs	Study Design	Key Findings
Dixit et al. (18), 2016	1,388	47	71.9 ± 5.0	NA	Observational study (24-h Holter)	<ul style="list-style-type: none"> No correlation between VPBs/h and intake of coffee (p = 0.86) or tea (p = 0.32). No correlation between VT runs and intake of coffee (p = 0.57) or tea (p = 0.13).
Zuchinali et al. (29), 2016	51	74	60.6 ± 10.9	NA	Randomized controlled trial	<ul style="list-style-type: none"> Acute caffeine ingestion (500 mg over 5 h) vs. placebo did not increase VPBs (185 vs. 239, respectively; p = 0.47) or nonsustained VT in patients with moderate to severe LV dysfunction.
Bertoia et al. (62), 2013	239/93,676	0	63.5 ± 7.4	11	Prospective cohort study	<ul style="list-style-type: none"> No association between total intake of caffeine (p for trend = 0.52), coffee (p for trend = 0.84), and caffeinated tea (p for trend = 0.30) and risk of SCD.
Klatsky et al. (23), 2011	323/1,30054	44	–	17.6	Retrospective population cohort	<ul style="list-style-type: none"> Higher coffee intake was not associated with higher risk of VT (HR: 1.05; 95% CI: 0.98 to 1.12), with a trend toward lower risk of ventricular fibrillation/SCD (HR: 0.88; 95% CI: 0.78 to 1.00).
de Vreede-Swagemakers et al. (36), 1999	117	84	65 ± 7	NA	Case control	<ul style="list-style-type: none"> Only very heavy coffee consumption (>10 cups per day) was associated with a higher risk of SCD (OR: 55.7; 95% CI: 6.4 to 483); however, 1–9 cups per day was not a significant predictor.
Graboyes et al. (28), 1989	50	76	61	NA	Crossover trial	<ul style="list-style-type: none"> In patients with structural heart disease, hourly VPB burden and nonsustained VT did not differ between the caffeine and placebo trials (despite elevated catecholamine levels in the caffeine arm).
Myers et al. (35), 1987	70	79	58 ± 2	NA	Randomized double-blind trial	<ul style="list-style-type: none"> In 7-day post-myocardial infarction patients, continuous Holter monitoring did not show a difference in percentage of patients who had VPBs, nor VPB burden after 300 mg of caffeine vs. placebo (despite rises in blood pressure and catecholamine levels in the caffeine group).
Prineas et al. (37), 1980	7,311	100	37-57	NA	Cross-sectional survey	<ul style="list-style-type: none"> Compared with consumption of ≤2 drinks per day, coffee (t = 2.90; p < 0.005) and tea (t = 3.78; p < 0.001) were positively associated with the presence of VPBs, with >9 cups of coffee associated with twice the risk of VPBs in healthy patients.

LV = left ventricle; SCD = sudden cardiac death; VPB = ventricular premature beats; VT = ventricular tachycardia; other abbreviations as in Table 2.

CONCLUSIONS

Many clinicians continue to counsel patients with atrial or VAs to avoid all caffeinated beverages, particularly coffee, despite an absence of evidence to support this approach. If, in individual cases where a clear temporal association between arrhythmia episodes and caffeine intake is apparent, then avoidance is sensible. Large-scale population-based studies and randomized controlled trials suggest coffee and tea

are safe and may even reduce the incidence of arrhythmia. Although there is no clearly defined threshold for caffeine harm, a regular intake of up to 300 mg/day appears to be safe and may even be protective against heart rhythm disorders.

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