Effect of caffeine on ventricular arrhythmia: a systematic review and meta-analysis of experimental and clinical studies

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Aims
The relationship between caffeine consumption and the occurrence of arrhythmias remains controversial. Despite this lack of scientific evidence, counselling to reduce caffeine consumption is still widely advised in clinical practice. We conducted a systematical review and meta-analysis of interventional studies of the caffeine effects on ventricular arrhythmias.

Methods and results
The search was performed on Pubmed, Embase, and Cochrane database, and terms related to coffee, caffeine, and cardiac arrhythmias were used. Methodological quality was assessed based on The Cochrane Collaboration recommendations and the ARRIVE guidelines. There were 2016 citations retrieved on the initial research. After full-text assessment, seven human and two animal studies were included in the meta-analysis. In animal studies, the main outcome reported was the ventricular fibrillation threshold. We observed a significant mean difference of $2.15 \text{ mA} \ (95\% \ CI \ 2.43 \text{ to } -0.87; \ I^2 \ 0.0\%, \ P \ for \ heterogeneity = 0.37)$. The main outcome evaluated in human studies was the rate of ventricular premature beats (VPBs). The overall relative risk for occurrence of VPBs in 24 h attributed to caffeine exposure was $1.00 \ (95\% \ CI \ 0.94 \text{ to } 1.06; \ I^2 \ 13.5\%, \ P \ for \ heterogeneity = 0.32)$. Sensitivity analysis for caffeine dose, different designs, and subject profile was performed and no major differences were observed.

Conclusion
Our meta-analysis demonstrates that data from human interventional studies do not show a significant effect of caffeine consumption on the occurrence of VPBs. The effects observed in animal studies are most probably the result of very high caffeine doses that are not regularly consumed in a daily basis by humans.

Keywords
Caffeine • Coffee • Arrhythmias

Introduction
Caffeine is the major component of coffee, tea, and some of the most consumed beverages worldwide. Caffeine (1,3,7-trimethylxanthine) is a naturally occurring purine that exert its biological effect through the antagonism of adenosine receptors (subtypes A1 and A2), resulting in a stimulatory property.¹,² The relationship between caffeine consumption and the occurrence of arrhythmias has been explored for many decades, but remains controversial.³,⁴

Early experimental studies indicated that caffeine appeared to cause severe ventricular arrhythmias.⁵ This pro-arrhythmic effect, however, has not been consistent in all animal studies, including reports that assessed dose-dependent protocols.⁶,⁷ Similarly, human studies have also been conflicting. Isolated case reports have suggested a direct association between caffeine consumption and sudden death, presumably mediated by severe ventricular arrhythmias.⁸ On the other hand, recent dose–response meta-analysis of cohort studies resulted in a counterintuitive protective effect of caffeine exposure on the risk of atrial fibrillation (AF).⁹

Small prospective clinical trials did not demonstrate an increase in clinically significant ventricular or supraventricular arrhythmias, even after exposure to high doses of caffeine.⁴ Moreover, studies in patients at risk of arrhythmia showed that moderate caffeine consumption apparently did not induce arrhythmic events.¹⁰ However,
there is no large-scale prospective randomized controlled trial that convincingly evaluate the effect of caffeine on the risk of arrhythmias. Despite this lack of strong scientific evidence, counselling to reduce caffeine consumption is still very tempting and widely used in clinical practice. In particular, drinking caffeine-rich beverages is often discouraged by physicians to patients presenting with a wide range of unspecific symptoms, such as palpitations, tachycardia, or irregular heartbeats, even in the absence of structural heart disease. Thus, the aim of this study was to systematically review the literature of animal and human interventional studies, and conduct a meta-analysis of the caffeine effects on ventricular arrhythmias, in healthy and unhealthy subjects.

**Methods**

For this systematic review and meta-analysis, we followed the Cochrane Collaboration methods and PRISMA statement.

**Search strategy and study selection**

Studies were identified through electronic database searches on Medline (accessed by Pubmed), Embase, and Cochrane Central Register of Controlled Trials database up to 05/2014, without update limits. In order to obtain a high-sensitivity strategy, the following search terms were used, both as free-text and subject headings: coffee, caffeine, arrhythmias, cardiac. Only eligible full texts in English, Portuguese, or Spanish were considered for review. The complete search strategy used for the PubMed database was (‘Arrhythmias, Cardiac’[Mesh] OR arrhythmia) AND ((coffee OR caffeine) OR (coffee[Mesh] OR ‘caffeine’[Mesh])).

**Eligibility criteria**

To comprehensively assess the association between arrhythmia and caffeine, we included interventional studies that evaluated caffeine alone and its effects on arrhythmia outcomes. Studies should show comparison data of groups of patients that did not receive caffeine or has received a matching placebo. Both animal and human reports, including healthy and unhealthy subjects were included. There was no restriction to study design, except for ex vivo models.

![Flow diagram](image-url)
### Table 1 Characteristics of the animal studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Animal model</th>
<th>n</th>
<th>Age</th>
<th>Weight</th>
<th>Dose (mg)</th>
<th>Duration of intervention</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| Bellet et al. | Experimental | Dogs         | 15                     | NR          | 25–30 pounds | 25 mg/kg  | Single administration    | VFT      | CF = 9.6 ± 6.0 mA\(^\ddagger\)  
CTL = 14 ± 0.72 mA        |
| Fusilli et al.| Experimental | Dogs         | 7 CF, 8 CTL            | 2 years     | CF:10.4 ± 0.33 kg  
CTL:9.9 ± 0.27 kg | 35 mg      | 30 min infusion        | VFT      | CF = 41.9 ± 1.3 mA  
CTL = 43.9 ± 1.3 mA        |
| Ilback et al. | Experimental | Rats         | 1 CF, low dose, mod. Dose, high dose | NR          | 300 g        | 5 mg/kg   | Single administration    | Arrhythmias | No effect associated to high dose of caffeine      |
| Ishida et al. | Experimental | Rabbits      | 5 CF, 5 low dose, 24 CF high dose | NR          | 2.5–3.3 kg   | 0.3 mg/kg/min  
1.0 mg/kg/min | Continuous infusion until outcome | Time to VPBs | CTL = No VPBs  
CF low dose = No VPBs  
CF high dose = 35 min |
| Mehta et al.  | Experimental | Dogs         | 13 animals that underwent:  
10 low CF\(^a\),  
16 mod. CF\(^a\),  
25 high CF\(^a\) | NR          | NR                       | 1.0 mg/kg  
2.5 mg/kg  
5.0 mg/kg | Single administration | VPBs  
\(n = 5\)  
\(n = 20\)  
\(n = 50\) |
| Rashid et al. | Experimental | Dogs         | 7 CF, 10 CF, 8 CF, 7 CF, 4 CF | NR          | 20–24 kg     | CTL\(^b\)  
2–4 μg/mL\(^b\),  
5–7 μg/mL\(^b\),  
8–10 μg/mL\(^b\),  
11–20 μg/mL\(^b\) | 3 subsequent doses with 2 min of interval | WOV for AF  
\(271 ± 85 \text{ ms}^\ddagger\)  
\(154 ± 114 \text{ ms}^\ddagger\)  
\(167 ± 55 \text{ ms}^\ddagger\)  
\(126 ± 32 \text{ ms}^\ddagger\)  
\(115 ± 84 \text{ ms}^\ddagger\) |

**Notes:**  
\(\text{CTL, control; CF, caffeine; VTF, ventricular fibrillation threshold; Mod., moderate; VPBs, ventricular premature beats; WOV, window of vulnerability.}\)  
\(\text{\(^a\)Number of experiments.}\)  
\(\text{\(^b\)Seric dosage of caffeine.}\)  
\(\text{\(^\ddagger P < 0.05\) compared with control group.}\)
Data extraction
Titles and abstracts were evaluated by two independent reviewers (P.Z. and P.A.B.R.) and any discrepancy was solved by consensus or by a third reviewer (L.E.R.). Reviewers were not blinded to author, institutions, or manuscripts journals. Abstracts that did not provide enough information were accepted for subsequent evaluation. The full-text analysis and data extraction were performed by the same two reviewers. For each study, we extracted information about publication data, population characteristics, intervention and comparison group, study protocol, outcomes, and limitations.

Assessment of bias risk and study quality
Methodological quality was explored using an approach similar to that recommended by The Cochrane Collaboration in assessing risk. Quality assessment and risk of bias for human studies included specific questions for clinical trials and cross-over designs. The following dimensions were considered: study design, sequence generation, allocation concealment, blinding, losses and exclusions, randomization, and carry-over effects. For animal studies, data selected for extraction were related to experimental procedures, animal characteristics, facilities and animal conditions, sample numbers, as described in Kilkenny et al. and the ARRIVE Guidelines. Risk judgement was assessed using pre-specified criteria about the adequacy of the study and expressed as ‘low risk’, ‘high risk’, or ‘unclear risk’. It was considered high risk of bias when the information was not provided at all. For animal studies, the bias and quality assessment was expressed as ‘Yes’, ‘No’, and ‘Unclear’ answers.

Data analyses
For each study, we looked for arrhythmic outcomes reported after caffeine intervention and control. Analyses were performed using a random-effects model. Statistical heterogeneity among studies was assessed using the $I^2$ statistic in which values >50% were considered indicative of high heterogeneity. Possible publication bias was evaluated with the Egger’s regression asymmetry test. We performed subgroup analysis for potential confounding factors. All statistical analyses were conducted using the Stata software version 11.0 (Stata Inc., College Station, TX, USA) with two-tailed α set at $P \leq 0.05$ for statistical significance.

Results
There were 2016 citations retrieved on the initial assessment. After full-text evaluation, 11 human and 6 animal studies were selected for the systematic review, and 7 human and 2 animal studies were selected for the meta-analysis. A flow diagram of the search and selection protocol is shown in Figure 1.

Animal studies
Description of studies
After full-text analysis, most of the excluded reports were due to the use of isolated hearts in the protocol. The number of animals in each experiment group varied from 1 to 24, including rats, dogs, and rabbits. Information extracted from included studies in qualitative and quantitative analysis is shown in Table 1. Five different arrhythmic-related outcomes were reported. In general, research protocols had an additional stimulatory phase and different doses of caffeine were compared. Overall, animal studies demonstrated a significant increase in arrhythmic outcomes after exposure to caffeine (Table 1).
Ilback et al.6, however, did not observe an association of high-dose caffeine (45 mg/kg) with the prevalence of arrhythmias in a rat model.

Quality and publication bias assessment
Description and methodology of animal protocols did not achieve high-quality standards in many important aspects. No animal study was blinded or randomized. Characteristics of the animals used in the protocols, such as age, weight, and gender, were not presented in many of the studies (Table 2). Two studies reported unbiased data, i.e. without possible carry-over effect. Only 50% of the studies had description of losses and exclusions and most of them did not report the number of animals in each part of the protocol.

Meta-analysis of animal studies
Only two experimental studies were included in the meta-analysis, both conducted in dogs (n = 35 animals). The outcome reported in both reports was the ventricular fibrillation threshold (VFT). Bellet et al.15 have reported results from different groups of animals; we have chosen the group that uses a comparable measure of VFT. Ventricular fibrillation threshold was expressed as mean of milliamps, measured 60 min after the acute intervention (Figure 2). The mean difference in VFT over the two studies was −2.15 mA (95% confidence interval [CI] −3.43 to −0.87; $I^2$ 0.0%, $P$ for heterogeneity = 0.37). The lack of a common arrhythmic-related outcome was the major reason that did not allow other studies to be included in the meta-analysis.

Human studies
Description of studies
A total of 11 human studies (n = 434 subjects) fulfilled the inclusion criteria for the systematic review and 7 were included in the meta-analysis (n = 290 subjects). Prakash and Kaushik18 was excluded from the final analysis because no patient had arrhythmia at the end of protocol. Characteristics of the 11 studies are summarized in Table 3. Four of these had a randomized cross-over design, three were double-blinded randomized clinical trials (RCTs), and four were classified as quasi-experiment trials, i.e. studies that had a comparison group or control period but did not fit the RCT design. Most of the studies included patients with some previous risk condition for arrhythmia, two included only healthy subjects and one report included both healthy and unhealthy populations. The study protocols were predominantly short-term interventions with a single dose of caffeine or matching control, although one study had a 2-week interventional period. Subjects were monitored by Holter or continuous electrocardiogram to evaluate arrhythmic-related outcomes.

Quality and publication bias assessment
None of the studies had a clear description of sequence generation, allocation concealment, and description of losses and exclusions. The studies with a cross-over design appropriately reported that the interventions were randomized. Only one cross-over study had unbiased data available, i.e. it reported the data from the first period of the protocol (Table 4).

Meta-analysis of human studies
The overall relative risk for occurrence of VPBs in 24 h after caffeine exposure was 1.00 (95% CI 0.94–1.06; $I^2$ 13.5%, $P$ for heterogeneity = 0.32). Sutherland et al. provided more than one interventional group and both were included and analysed separately. We performed sensitivity analysis for study design, caffeine dose (< and $\geq$ 300 mg) and subject condition (healthy and unhealthy status) (Figures 3–5). Overall, none of these analyses provided different results, although we observed increased heterogeneity in

<table>
<thead>
<tr>
<th>Source</th>
<th>Weighted mean difference (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusilli et al., 1989</td>
<td>−2.00 (−3.32, −0.68)</td>
<td>94.08</td>
</tr>
<tr>
<td>Bellet et al., 1972</td>
<td>−4.50 (−9.76, 0.76)</td>
<td>5.92</td>
</tr>
<tr>
<td>$I^2 = 0.0%$. $P$ for heterogeneity = 0.366</td>
<td>−2.15 (−3.43, −0.87)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2 Absolute changes in the VFT of animal studies comparing caffeine vs. control.
Table 3  Characteristics of the human studies

<table>
<thead>
<tr>
<th>Study</th>
<th>SD</th>
<th>Condition</th>
<th>n</th>
<th>Age</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration of intervention</th>
<th>Outcome</th>
<th>Other relevant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheslky et al.</td>
<td>1 day/1 group</td>
<td>Symptomatic VT or VF</td>
<td>22</td>
<td>60 ± 10</td>
<td>275 mg + electrical stimulation</td>
<td>Control period without caffeine</td>
<td>Single dose</td>
<td>Inducibility and severity scores</td>
<td>–</td>
</tr>
<tr>
<td>Grabosy et al.</td>
<td>1 day/2 groups</td>
<td>Malignant VA</td>
<td>50</td>
<td>NR</td>
<td>200 mg</td>
<td>Decaffeinated coffee</td>
<td>Single dose</td>
<td>VPBs</td>
<td>VT CF: 6 ± 24 CTL: 6 ± 24</td>
</tr>
<tr>
<td>Lemery et al.</td>
<td>RCT</td>
<td>Symptomatic SVT</td>
<td>80</td>
<td>49 ± 14</td>
<td>5 mg/kg + electrical stimulation</td>
<td>Placebo</td>
<td>Single dose</td>
<td>VT</td>
<td>SVT cycle length CF: 314 (286–382) CTL: 314 (280–360) No VT</td>
</tr>
<tr>
<td>Myers and Harris</td>
<td>Cross-over</td>
<td>Previous AMI</td>
<td>70</td>
<td>64 ± 2</td>
<td>300 mg</td>
<td>Placebo lactose powder</td>
<td>2 doses with 4 h of interval</td>
<td>VPBs</td>
<td>Patients with VT CF: 1 CTL: 0</td>
</tr>
<tr>
<td>Myers et al.</td>
<td>Cross-over</td>
<td>Previous AMI</td>
<td>35</td>
<td>58 ± 2</td>
<td>450 mg</td>
<td>Placebo lactose powder</td>
<td>Single dose</td>
<td>VPBs</td>
<td>Patients with VT CF: 1 CTL: 0</td>
</tr>
<tr>
<td>Newby et al.</td>
<td>Cross-over</td>
<td>Symptomatic palpitations and frequent VPBs</td>
<td>13</td>
<td>NR</td>
<td>Minimum 3 cups/day</td>
<td>Decaffeinated coffee</td>
<td>1 week for each protocol</td>
<td>VPBs</td>
<td>–</td>
</tr>
<tr>
<td>Newcombe et al.</td>
<td>2 days/1 group</td>
<td>Healthy</td>
<td>34</td>
<td>31 (21–49)</td>
<td>1 mg/kg/half life</td>
<td>Control period without caffeine</td>
<td>24 h</td>
<td>VPBs</td>
<td>SVPBs CF: 3 ± 4 CTL: 5 ± 11</td>
</tr>
<tr>
<td>Prakash and Kaushik</td>
<td>Cross-over</td>
<td>Healthy</td>
<td>12</td>
<td>25–39</td>
<td>175 mg</td>
<td>Decaffeinated coffee</td>
<td>Single dose</td>
<td>Arrhythmia</td>
<td>–</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>RCT</td>
<td>Type 1 diabetic patients and healthy controls</td>
<td>30</td>
<td>NR</td>
<td>250 mg</td>
<td>Matched placebo</td>
<td>2 weeks for each protocol</td>
<td>VPBs</td>
<td>No effect associated to VT SVPB or SVT</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>RCT</td>
<td>Previous STEMI</td>
<td>52</td>
<td>CTL: 67.4 ± 12.1 CF: 67.8 ± 10.6</td>
<td>Decaffeinated coffee</td>
<td>5 days</td>
<td>VPBs</td>
<td>VT CF: 5.3% CTL: 2.9% SVPB CF: 2.6% CTL: 2.9%</td>
<td></td>
</tr>
<tr>
<td>Sutherland et al.</td>
<td>2 days/1 group</td>
<td>Healthy subjects with VPBs</td>
<td>36</td>
<td>Healthy: 32 ± 7 VPBs: 39 ± 11</td>
<td>1 mg/kg/half life</td>
<td>Control period without caffeine</td>
<td>24 h</td>
<td>VPBs</td>
<td>Patients with VT CF: 1 CTL: 0</td>
</tr>
</tbody>
</table>

SD, study design; CTL, control group; CF, caffeine group; NR, not reported; VT, ventricular tachycardia; VF, ventricular fibrillation; VA, ventricular arrhythmia; SVT, supraventricular tachycardia; SVPBs, supraventricular ectopic beats; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VPBs, ventricular premature beats.

aNot randomized intervention.
bConsumption average.
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). Sensitivity analysis was also performed excluding a study that involved an exercise phase as a second intervention and one study evaluating a chronic intervention of caffeine. Again, no major differences in the main results were observed.

**Discussion**

Caffeine-rich beverages have been traditionally considered the main culprit environmental factor implicated in a variety of ordinary but unspecific complaints (like palpitations and heartbeat irregularities) in clinical practice. Physicians are particularly worried that these symptoms might be mediated by potentially dangerous arrhythmic events. In this scenario, case reports have linked caffeine overdose to ventricular and supraventricular arrhythmias. In addition, fatal ingestion of the substance has been described (usually with doses over 5 g), which reinforced the hypothesis of a positive cause and effect relationship between caffeine intake and arrhythmias.

The present systematic review and meta-analysis was specifically designed to address the impact of prospective interventions using coffee or caffeine supplements compared with a matching control on the incidence of ventricular arrhythmias. We have demonstrated that although animal studies suggest that high-dose caffeine might reduce the threshold for several types of arrhythmias, human studies consistently failed to show and increased risk for ventricular arrhythmias.

Initial experimental studies in dogs in the early 1970s and 1980s have raised the concern about the association of caffeine use and the risk of severe ventricular arrhythmic events. Two of these studies were meta-analysed in the present report, demonstrating an increased risk to develop ventricular fibrillation in animals that received very high doses of caffeine (up to 35 mg/kg). Similarly, Ishida et al. have shown that a high-dose continuous infusion of caffeine (1 mg/kg/min) was associated with the appearance of ventricular ectopic beats in rabbits, while Mehta et al. demonstrated a dose–response effect on the occurrence of VPBs after a single dose of caffeine in dogs. Except for Ilback et al., all animal models were consistent to demonstrate a positive and significant association with arrhythmic outcomes, including vulnerability to AF. The results in animal studies that could not be meta-analysed showed a possible dose–effect relationship, as we observe in the experiments performed by Rashid et al., in which the time to the arrhythmic outcome decreased with increasing blood concentration of caffeine. However, human studies analysing coffee intake, the most common source of ingestion of caffeine, did not confirm this behaviour. In a recent meta-analysis of prospective studies that examined dose–response effect of usual intake of coffee, it has been shown that the risk of developing AF decreases by 6% for each increase of habitual intake of 300 mg of coffee, leading us to consider that usual intake of caffeine may even be protective against arrhythmic outcomes. On the other hand, fatal doses of caffeine have been reported in the literature. New prospective well-designed animal studies that evaluate progressive doses of caffeine (from very low to very high) in different scenarios (healthy and post-myocardial infarction) are needed to elucidate this hypothesis.

### Table 4 Quality assessment of human studies

<table>
<thead>
<tr>
<th>Study</th>
<th>SD</th>
<th>RSG</th>
<th>AC</th>
<th>Description of LE</th>
<th>Blinding of OA</th>
<th>Blinding of PP</th>
<th>C-O design appropriate?</th>
<th>The order of treatments was randomized?</th>
<th>No carry-over bias effects?</th>
<th>Are unbiased data available?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest et al.</td>
<td>RCT</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Grabois et al.</td>
<td>RCT</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Myers and Harris</td>
<td>C-O</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Myers et al.</td>
<td>C-O</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Newcomb and Kasinski</td>
<td>C-O</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Richardson</td>
<td>C-O</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Sutherland</td>
<td>C-O</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

SD, study design; RSG, random sequence generation; AC, allocation concealment; OA, outcome assessment; PP, participants and personnel; LE, losses and exclusions; C-O, crossover.
In addition, large epidemiologic studies did not demonstrate a significant association of caffeine intake with increased rates of arrhythmias. Similarly, a recent meta-analysis of seven observational studies evaluated the association between chronic exposure to caffeine and AF in more than 100,000 individuals. Overall, caffeine exposure was not associated with an increased risk of AF. Interestingly, pooled results from high-quality studies showed a 13% odds reduction in AF risk, particularly after low-dose caffeine exposure.
Unhealthy

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myers et al., 1990</td>
<td>1.23 (0.78, 1.92)</td>
<td>1.44</td>
</tr>
<tr>
<td>Myers et al., 1987</td>
<td>1.26 (0.97, 1.63)</td>
<td>4.13</td>
</tr>
<tr>
<td>Sutherland et al., 1985a</td>
<td>0.69 (0.36, 1.30)</td>
<td>0.73</td>
</tr>
<tr>
<td>Richardson et al., 2009</td>
<td>0.98 (0.93, 1.03)</td>
<td>48.88</td>
</tr>
<tr>
<td>Newby et al., 1996</td>
<td>0.64 (0.30, 1.36)</td>
<td>0.51</td>
</tr>
<tr>
<td>Graboys et al., 1989</td>
<td>0.93 (0.66, 1.31)</td>
<td>2.99</td>
</tr>
</tbody>
</table>

$I^2 = 38.7\%; P$ for heterogeneity = 0.148

Healthy

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutherland et al., 1985b</td>
<td>1.00 (0.86, 1.16)</td>
<td>11.50</td>
</tr>
<tr>
<td>Newcombe et al., 1998</td>
<td>1.00 (0.92, 1.08)</td>
<td>30.34</td>
</tr>
</tbody>
</table>

$I^2 = 0\%; P$ for heterogeneity = 1.000

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graboys et al., 1989</td>
<td>1.00 (0.94, 1.06)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

$I^2 = 13.5\%; P$ for heterogeneity = 0.325

0.299 Ventricular premature beats (24h) 3.34

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myers et al., 1990</td>
<td>1.23 (0.78, 1.92)</td>
<td>1.44</td>
</tr>
<tr>
<td>Myers et al., 1987</td>
<td>1.26 (0.97, 1.63)</td>
<td>4.13</td>
</tr>
<tr>
<td>Sutherland et al., 1985a</td>
<td>0.69 (0.36, 1.30)</td>
<td>0.73</td>
</tr>
<tr>
<td>Richardson et al., 2009</td>
<td>0.98 (0.93, 1.03)</td>
<td>48.88</td>
</tr>
<tr>
<td>Newby et al., 1996</td>
<td>0.64 (0.30, 1.36)</td>
<td>0.51</td>
</tr>
<tr>
<td>Graboys et al., 1989</td>
<td>0.93 (0.66, 1.31)</td>
<td>2.99</td>
</tr>
</tbody>
</table>

$I^2 = 38.7\%; P$ for heterogeneity = 0.148

Figure 5 Relative risk for VPBs in 24 h of human studies comparing caffeine vs. control by subject condition.

Limitations

Some limitations of the current analysis deserve consideration. We acknowledge that data relating caffeine consumption and risk of arrhythmias are still incomplete. Individual studies are small-sized with poor methodological quality. Internationally accepted quality parameters of the included studies were consistently faulty for both animal and human reports, with omission of important information regarding protocol description, allocation of interventions, and baseline characteristics of research subjects. A recent meta-analysis that evaluated the effect of caffeine on intraocular pressure also reported methodological limitations. In the current analysis, we observed increased heterogeneity in most subgroup analysis (Figures 3–5).

Furthermore, studies evaluating the effect of energy drinks on arrhythmia could not be included in the current protocol, since it would not be possible to isolate the effect of caffeine. This type of beverage usually contains high concentrations of taurine, vitamins, herbal supplements, and sugar or sweeteners. High doses of taurine have been associated with an increased risk of atrial and ventricular arrhythmias or cardiac arrest, which could be an important confounder factor.

Conclusion

Our systematic review and meta-analysis demonstrates that compilation of data from human interventional studies does not identify any meaningful interaction between caffeine consumption in different doses and VPBs. The effects found in animal studies are most probably the result of caffeine doses that are not consumed in regular daily basis in humans. Despite these evidences, a survey of

(odds ratio 0.85, 95% CI 0.78–92, $I^2 = 0\%$).

This counterintuitive protective effect was attributed to a J-shaped curve, a phenomenon that has been previously described between coffee consumption and risk of heart failure. O’Keefe et al. recently reviewed the effects of coffee consumption on overall cardiovascular health. They concluded that there is a growing body of observational evidence suggesting that habitual coffee consumption is neutral to beneficial regarding the risks of a variety of cardiovascular outcomes. Furthermore, population-based studies indicate that a daily intake of ~2–3 cups of coffee appears to be safe and does not increase the risk of arrhythmias.

Human studies included in this systematic review and meta-analysis used either coffee or caffeine supplements as the main intervention, in doses consistent with real life use, although most reports assessed acute or short-term protocols. It is important to point out that most studies had small samples ($n < 40$ subjects) and could not provide a definitive answer, making useful and necessary the compilation of these data. The final result of our meta-analysis did not reveal any significant overall effect of coffee or caffeine supplements on the rates of VPBs in humans. The differences in protocols, populations (healthy or at risk for arrhythmias), dose of caffeine, and study design were analysed separately and the main results were not changed.

Few studies have evaluated the effects of different ways of preparing coffee (filtered or not) or intravenous administration of caffeine on cardiovascular outcomes. Instead, most reports have demonstrated that caffeine can impair the absorption of several nutrients. A pharmacological study compared different ways of caffeine ingestion (capsule, coffee, and cola). Peak caffeine absorption, time to peak absorption, and subjective effects did not appear to be substantially influenced by the type of vehicle.

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Conclusion

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medical personnel indicate that more than 75% of the specialists recommended reduction in caffeine in patients with anxiety, arrhythmias, palpitations, and tachycardia. Our data reinforce the concept that there is no scientific reasoning that supports a clin-
cial recommendation to decrease or avoid caffeine consumption in 
patients at risk or with suspicious symptoms of arrhythmias. How-
ever, further high-quality prospective studies are warranted to 
clearly address the impact of coffee consumption on the risk of 
arrhythmias.

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