

# Caffeine and Cardiac Arrhythmias: A Review of the Evidence

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## ABSTRACT

Limited data exist on the safety and physiologic effects of caffeine in patients with known arrhythmias. The studies presented suggest that in most patients with known or suspected arrhythmia, caffeine in moderate doses is well tolerated and there is therefore no reason to restrict ingestion of caffeine. A review of the literature is presented.

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**KEYWORDS:** Arrhythmia; Caffeine

Over half of Americans drink coffee daily, and more ingest caffeine in either coffee or another form such as tea, soda, and chocolate.<sup>1,2</sup> The topic of the effects of caffeine on the cardiovascular system has been a source of much debate. Case reports have linked caffeine overdose to coronary vasospasm<sup>3</sup> and a variety of supraventricular<sup>4,5</sup> and ventricular<sup>5,6</sup> arrhythmias. A survey of 697 providers revealed that 80%-90% recommended moderating caffeine intake in patients with known tachycardia, palpitations, and arrhythmia,<sup>7</sup> yet it is unclear from where this impressive consensus arises. A common question in the care of patients with known arrhythmia is the safety of caffeine and whether there is a need to curtail caffeine intake.

Currently, our limited understanding is based on case reports, cohort studies, physiologic studies, and large epidemiologic studies. Case reports must be cautiously considered due to the inherent bias of reporting only cases in which caffeine ingestion was coincident with an arrhythmia; these do not demonstrate causality. Cohort studies that evaluate this topic examine at-risk populations such as those with known ventricular arrhythmias, but the number of

subjects is small, making it difficult to draw conclusions. Physiologic studies provide insights into the effects of caffeine on the cardiac conduction system, but study designs do not necessarily translate into true conditions. Epidemiologic studies evaluate healthy but not at-risk populations. Unfortunately, there are no large-scale randomized controlled trials on the effect of caffeine in populations of patients with arrhythmias.

The purpose of this article is to review the evidence relating caffeine and arrhythmia in order to provide an understanding of our knowledge and the limitations of our knowledge, as well as to provide recommendations for patients with known or suspected arrhythmia with regard to caffeine intake.

## CAFFEINE AND CARDIOVASCULAR DISEASE

Caffeine is a nonselective competitive antagonist of adenosine receptor subtypes A<sub>1</sub> and A<sub>2A</sub> in concentrations typically consumed by humans. At higher concentrations, caffeine can induce intracellular calcium release and phosphodiesterase inhibition, and at higher doses not typically consumed, can cause gamma-aminobutyric acid inhibition.<sup>8</sup> It is suggested that 100 mg can increase alertness in humans. Increases in blood pressure are noted at 250 mg, and the lethal dose has been estimated to be 10 g.<sup>9</sup> A cup of drip coffee typically provides 115-175 mg of caffeine, while instant coffee contains 65-100 mg.<sup>1</sup> The average consumption ranges from 200-300 mg/day in the United States.<sup>2,10</sup>

Several human studies have examined the effect of caffeine use on cardiovascular disease. A 1965 cohort study of

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5858 Japanese men found a relationship between caffeine use and serum cholesterol, but the difference between those consuming no coffee and those consuming 7 or more cups per day was only 13 mg/dL.<sup>11</sup> A recent study revealed no association between caffeine and coronary artery calcium score, carotid intima-media thickness, or progression of atherosclerotic lesions in a population of 5115 adults aged 18-30 years.<sup>12</sup> Additionally, in a study in which exercise stress tests were performed on patients with coronary artery disease, caffeine (250 mg) was shown to have no effect on exercise duration, time to onset of angina, and time to onset of ST-segment depression, although peak blood pressure increased by 7 mmHg.<sup>13</sup> Further echocardiographic evaluation in this study showed no effect on left ventricular function.

Studies have shown that caffeine increases blood pressure and catecholamine levels, and lowers heart rate after acute ingestion<sup>14-17</sup>; although energy drinks can have differential effects on the heart rate, possibly due to other substances.<sup>18</sup> However, the blood pressure effect resolves within 4 hours in most patients.<sup>17</sup> Furthermore, these effects are attenuated in habitual coffee drinkers, suggesting that there is tolerance to the adrenergic effects.<sup>19</sup> In fact, habitual caffeine use has been shown to have minimal effect on long-term blood pressure.<sup>20</sup> Interestingly, the physiologic effects of caffeine differ in men and women.<sup>21</sup>

Large outcome-based studies of caffeine have been performed in humans. A 1990 2-year cohort study of 45,589 healthy men found no increased risk of myocardial infarction, stroke, or need for coronary revascularization in patients who drank coffee, even 4 or more cups per day.<sup>10</sup> Another group has performed multiple large epidemiologic studies finding no increased risk of coronary artery disease, stroke, or mortality with coffee consumption in cohorts of both healthy and diabetic subjects.<sup>22-24</sup> A 2007 study even found a dose-dependent beneficial effect of caffeine on cardiovascular mortality in the elderly, with a 52% reduction in risk in those consuming 4 or more servings per day.<sup>25</sup>

Overall, these studies are consistent, with minimal to no effect of caffeine on coronary artery disease or stroke. To examine the potential role of caffeine on arrhythmias, the following sections will explore its effects on the conduction system and arrhythmias in animals and humans.

## EFFECTS OF CAFFEINE ON THE HUMAN ELECTROCARDIOGRAM

Donnerstein et al<sup>26</sup> performed signal-averaged electrocardiograms (ECGs) in 12 subjects given a 5 mg/kg dose of caffeine. Compared with placebo, there was an increase in

QRS duration with caffeine ingestion; the small magnitude of this change, approximately 1 ms, is likely clinically insignificant, although it reached statistical significance. P-wave duration and heart rate remained unchanged. Caron et al<sup>27</sup> performed a study in which 10 healthy volunteers were

given caffeine (400 mg) and underwent ECG. Compared with the baseline ECG, there was no change in P-wave indices. The same group performed a similar study in which they showed that caffeine (400 mg) did not change electrocardiographic parameters, including PR interval, QRS duration, corrected QT interval, RR interval, or corrected QT interval dispersion.<sup>14</sup> Furthermore, when healthy volunteers drank a high-caffeine "energy drink," electrocardiographic parameters (except for heart rate) were unchanged.<sup>18</sup>

### CLINICAL SIGNIFICANCE

- Many physicians recommend avoidance of caffeine in patients with heart disease.
- Animal studies suggest that caffeine does have an effect on the cardiac conduction system at high doses.
- Large human studies generally reveal no association between caffeine and arrhythmias.

## ANIMAL STUDIES OF CAFFEINE AND ARRHYTHMIA

Animal studies allow investigators to probe the link between caffeine and arrhythmia in ways that are impossible using human subjects. Higher-dose caffeine protocols are typically used. Additionally, invasive studies and evaluations of the concomitant effects of ischemia that would be impossible to perform on human subjects are frequently employed. Bellet et al<sup>28</sup> performed a pivotal study in 1972 examining the effect of caffeine on the ventricular fibrillation threshold. In this experiment, the supraphysiologic caffeine dose of 12.5 mg/kg was injected into dogs, and the amount of energy required to induce ventricular fibrillation by delivering sequential impulses during the QT segment was determined. Caffeine decreased the ventricular fibrillation threshold in nonischemic and ischemic models in this study. This was seen as evidence that caffeine could induce or lower the threshold for arrhythmia in susceptible patients. Interestingly, the change in ventricular fibrillation threshold was prevented by beta blockade. In a rabbit study, high (1 mg/kg/min) but not moderate (0.3 mg/kg/min) doses of caffeine facilitated induction of ventricular tachycardia when animals were subjected to a ventricular pacing protocol, demonstrating a dose-dependent effect of caffeine on initiation of ventricular tachycardia.<sup>29</sup> Again, caffeine administration was accompanied by a large increase in plasma norepinephrine, and propranolol (as well as verapamil and adenosine) suppressed induction of ventricular tachycardia. In another study, increasing doses of caffeine (1-5 mg/kg) were given to dogs, resulting in increased incidence of both supraventricular and ventricular arrhythmias.<sup>30</sup> Ventricular tachycardia, atrial flutter, and atrial fibrillation were present only with high doses. Another study used programmed electrical stimulation in mice, finding that 1 mM of caffeine

introduced into a buffer perfusing the heart increased the incidence of ventricular tachycardia from 0% to 100%.<sup>31</sup> The role of triggered activity was suggested based on the response to diltiazem. Further evaluating the mechanism of the link between caffeine and arrhythmia, Pasma and Vassalle<sup>32</sup> performed a canine study in 1984 that recognized that caffeine induces an oscillatory potential in the Purkinje fibers that increases with concentration of caffeine and time of exposure. In this animal model, caffeine also increased the rate of spontaneous discharge in active fibers, and was seen to initiate spontaneous repetitive activity. Other mechanistic insights were provided by a study in which rats were injected with toxic doses of caffeine-sodium salicylate (15 mg/kg/min) and died with progressive ventricular ectopy starting at 22.8 minutes, eventually leading to ventricular fibrillation, an effect that was stalled but not ameliorated by beta-adrenergic or calcium-channel blockade.<sup>33</sup> All these data support the notion that at high doses, caffeine may produce catecholamine-induced triggered activity.

Although several studies have shown a proarrhythmic effect of caffeine in high doses, there also are animal studies that have shown no effect or a favorable effect of caffeine on the inducibility of arrhythmias. For example, in one study, dogs were given escalating doses (1-5 mg/kg) of caffeine and then underwent premature stimulation from the right superior pulmonary vein with and without low-level stimulation of ganglionated plexi at the entrance of the right superior pulmonary vein.<sup>34</sup> The window of vulnerability, a measure of the inducibility of atrial fibrillation, decreased

with increasing doses of caffeine. Another study of rats that underwent occlusion of the left main coronary artery for 30 minutes followed by reperfusion revealed that the incidence of ventricular arrhythmias during ischemia and reperfusion was decreased in the presence of caffeine.<sup>35</sup> However, another study in rats in which caffeine was injected during ischemia or reperfusion showed no change in the incidence of ventricular fibrillation.<sup>36</sup>

These studies support the idea that very high doses of caffeine in animals may be associated with ventricular arrhythmias, likely due to catecholamine-induced triggered activity.

## HUMAN STUDIES OF CAFFEINE AND ARRHYTHMIA

Several human studies have been performed to investigate the effect of caffeine on atrial and ventricular arrhythmias (Table).<sup>37-47</sup> Both physiologic and epidemiologic studies have been performed.

Early human studies were performed using invasive electrophysiology studies. Gould et al<sup>48</sup> obtained His bundle electrograms in 12 patients with known cardiovascular disease before and after ingestion of a 150-mg dose of caffeine.<sup>48</sup> There were no changes in intra-atrial, atrioventricular (AV) nodal, and His-Purkinje conduction. However, the effective and functional refractory periods of the AV node decreased after ingestion of coffee, an effect that was attributed to release of catecholamines. Dobmeyer et al<sup>49</sup>

**Table** Human Studies Examining the Effect of Caffeine on Arrhythmia

Reference	Year	n	Description
Frost and Vestergaard <sup>37</sup>	2005	47,949	No increased risk of atrial fibrillation or flutter in healthy patients followed for an average of 5.7 years
Conen et al <sup>38</sup>	2010	33,638	No increased risk of atrial fibrillation in healthy women followed for an average of 14.4 years
Prineas et al <sup>39</sup>	1980	7311	Ingestion of >9 cups of coffee per day associated with twice the risk of PVC in healthy patients
de Vreede-Swagemakers et al <sup>40</sup>	1999	117	Ingestion of >10 cups of coffee per day associated with OR of 55.7 for sudden cardiac death in population with coronary artery disease
DeBacker et al <sup>41</sup>	1979	81	No decrease in PVC frequency with avoidance of caffeine in healthy men with symptomatic PVC
Myers et al <sup>42</sup>	1987	70	No increase in ventricular arrhythmias in patients given 300 mg caffeine with recent MI as compared with placebo
Clee et al <sup>43</sup>	1979	50	No increase in ectopy with caffeine ingestion in elderly patients with high prevalence of baseline ectopy
Graboyes et al <sup>44</sup>	1989	50	No increase in arrhythmias with caffeine during stress test in patients with known ventricular arrhythmias
Myers and Harris <sup>45</sup>	1990	35	No increase in ventricular arrhythmias in patients given 450 mg caffeine with recent MI as compared with placebo
Sutherland et al <sup>46</sup>	1985	18	Increased frequency of PVC in patients with frequent PVC at baseline
Newby et al <sup>47</sup>	1996	13	No decrease in symptoms or frequency of PVC with avoidance of caffeine in patients with symptomatic PVC

PVC = premature ventricular complex; OR = odds ratio; MI = myocardial infarction.

found that 200 mg of caffeine shortened the refractory periods of the right atrium, AV node, and right ventricle. Paradoxically, the effective refractory period of the left atrium increased with caffeine. Of note, there was an increase in sustained atrial arrhythmias in response to programmed atrial extrastimuli after ingestion of caffeine, an effect that was noted in patients who reported caffeine sensitivity. However, the stage of the stimulation protocol at which the arrhythmias were induced was not indicated, and therefore the absolute sensitivity of these patients to caffeine cannot be clearly defined.

Further studies have administered caffeine to populations of patients followed with continuous electrocardiography. A 1985 study in 18 patients with frequent premature ventricular complexes (PVC) and 18 controls found that when patients were given caffeine at a dose of 1 mg/kg each half-life for a 24-hour period, those with frequent PVCs at baseline had an increase in the number of PVC/hour from  $207 \pm 350$  PVC/hour to  $307 \pm 414$  PVC/hour, while controls did not have an increase in ectopy.<sup>46</sup> A randomized, double-blinded physiologic study was performed in which 70 patients were given a 300-mg dose of caffeine within 7 days of myocardial infarction.<sup>42</sup> Although epinephrine levels increased and the systolic blood pressure increased, there was no increase in frequency or severity of ventricular arrhythmias in these high-risk patients. A later study administered either higher-dose (450 mg) caffeine or placebo to 35 patients with recent myocardial infarction and observed with 24-hour electrocardiography.<sup>45</sup> No increase in ventricular ectopy or arrhythmia was noted. Another study of 50 patients with known malignant ventricular arrhythmias who underwent bicycle stress testing with ingestion of caffeine (200 mg) showed no increase in ventricular arrhythmias.<sup>44</sup> Chelsky et al<sup>50</sup> performed invasive electrophysiologic studies in 22 patients with a history of symptomatic nonsustained ventricular tachycardia. These patients underwent electrophysiology study 1 hour before and after caffeine ingestion. This study showed that caffeine did not significantly alter inducibility or severity of arrhythmias, suggesting that caffeine has little effect on the substrate supporting ventricular arrhythmias. Thus, despite increases in epinephrine levels, these studies demonstrate no proarrhythmic effect of caffeine. It is interesting to note that although epinephrine levels increase with caffeine ingestion, the magnitude of the release is 6-fold less elevated than the increase noted during exercise.<sup>51</sup>

Several human epidemiologic studies have been performed to probe the link between caffeine and arrhythmia, with mixed results. An epidemiologic survey of 7311 healthy men aged 37-57 years who underwent 2-minute electrocardiographic recording revealed that drinking >9 cups of coffee per day was associated with twice the risk of PVCs after adjusting for other risk factors.<sup>39</sup> A self-reported questionnaire associated caffeine with triggering of right ventricular outflow tract tachycardia in men, but not in women.<sup>52</sup> A retrospective case-control study of 117 patients with a history of coronary artery disease who suffered

sudden cardiac arrest revealed an impressive association of heavy coffee consumption (>10 cups per day) with increased risk of sudden cardiac death, with an odds ratio of 55.7 (95% confidence interval, 6.4-483) compared with matched controls with coronary artery disease.<sup>40</sup> However, only 2 of the control subjects drank more than 10 cups of coffee per day, and therefore the size of the control group may have been inadequate. Larger-scale epidemiologic studies have been performed showing no association of caffeine intake with increased arrhythmias. In the Danish Diet, Cancer, and Health study, 47,949 subjects with a mean age of 56 years were followed on average for 5.7 years.<sup>37</sup> This study found no association between caffeine use and development of atrial arrhythmias. In the Women's Health Study, in which 33,638 women were followed for an average of 14.4 years, caffeine consumption also was not associated with an increased incidence of atrial fibrillation.<sup>38</sup> A trial of 81 healthy men with frequent PVCs who abstained from caffeine found no change in frequency of PVC as measured by 24-hour electrocardiography.<sup>41</sup> Additionally, in a study of 50 healthy elderly subjects followed by a continuous ECG, caffeine was not linked to an increase in atrial or ventricular ectopy despite a high prevalence of baseline ectopy in the study population.<sup>43</sup> Furthermore, a randomized trial of 13 patients with symptomatic idiopathic PVC compared the management of these patients with and without caffeine restriction and found no change in frequency of ectopic complexes or symptoms with avoidance of caffeine.<sup>47</sup> The disparities in these reports may relate to the arrhythmias evaluated, the underlying cardiac substrate, or methodologic issues.

## DISCUSSION AND RECOMMENDATIONS

With the conflicting data that are available, it is understandable that most physicians are unsure of the advice they can provide about caffeine intake and arrhythmias. A common idea in practice is that caffeine intake should be limited in patients at risk for arrhythmia; however, it is unclear what evidence provides support for this. Although this advice is frequently given to patients,<sup>7</sup> many of the data that have been reviewed suggest that this advice is unnecessary.

Although animal studies have shown a proarrhythmic effect of caffeine, this effect typically appears at much higher doses than consumed by human subjects, and has only been documented in abnormal clinical situations such as programmed stimulation and massive ischemia. Although these studies provide insights into the physiologic effects of caffeine on the cardiac conduction system, they do not provide real-world experience in patients who consume typical doses of caffeine.

Human studies have shown that caffeine has minimal effect on the ECG. Invasive electrophysiology studies have shown that there is an effect of caffeine on the refractory periods of atrial, ventricular, and nodal tissue,<sup>48,49</sup> however it is uncertain if these findings translate into a susceptibility for arrhythmia. Given the results of large human epidemi-



ologic studies, it is unlikely that the majority of patients are sensitive to the effects of caffeine. Nevertheless, there may be individuals who are susceptible to the small electrophysiologic changes induced by caffeine and therefore may experience arrhythmias with caffeine.

Although it has been shown that patients with frequent ventricular ectopy can have an increase in frequency of their arrhythmia with caffeine ingestion,<sup>46</sup> high-risk patients such as those with recent myocardial infarction,<sup>42,45</sup> nonsustained ventricular tachycardia,<sup>43</sup> and malignant ventricular arrhythmia<sup>44</sup> have been studied with no increase in frequency or severity of arrhythmia. These studies provide evidence that caffeine may not be harmful even in patients who are at risk of malignant arrhythmia.

There are significant limitations in our knowledge about the relationship between caffeine and arrhythmia. Although large-scale epidemiologic human studies do exist, they did not study patients with malignant arrhythmias. Therefore, we rely on smaller studies to make inferences about outcomes in these patients. Several studies did evaluate the arrhythmias of interest; they were limited by a short time period of results and therefore cannot capture infrequent outcome events. In addition, specific arrhythmias such as catecholaminergic polymorphic ventricular tachycardia have not been studied, although survey evidence exists to suggest that caffeine increases the frequency of right ventricular outflow tract tachycardia.<sup>52</sup> Patients who state that their arrhythmias are triggered by caffeine intake have not been studied in adequate depth to draw conclusions about the safety of caffeine ingestion. In these cases, it is prudent to abstain from caffeine until further information is available.

Overall, the data suggest that in most patients, even those with known or suspected arrhythmia, caffeine in moderate doses is well tolerated and there is therefore no reason to restrict ingestion of caffeine. Care should be taken to avoid caffeine in situations in which catecholamines are thought to drive the arrhythmia, as well as in patients who note sensitivity to caffeine.

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