

# Coffee Consumption and Cardiovascular Disease Risk: What Should We Tell Our Patients?

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The association between coffee and the risk of cardiovascular disease has been studied over the past 20 years. Given the complexity of conducting large, randomized, controlled trials to prove causality, conclusions are based on case reports, retrospective studies, and small physiologic trials. Surveys determine that most physicians advise discontinuing or reducing consumption of caffeine in patients with known heart disease, yet this recommendation lacks strong supporting evidence. The following is a short review of the effects of coffee and caffeine on the cardiovascular system that aims to provide objective advice to physicians and patients based on the published literature.

*Hypothetical Case: A 40-year-old female with no significant past medical history presents to your primary care clinic for a routine checkup. She complains of intermittent palpitations and believes that she has a life-threatening cardiac condition because her brother died of a heart attack at a young age. After obtaining a detailed history, you find that she has been under a lot of stress and has been consuming six to seven cups of coffee per day for the past several weeks. Her exam is benign and her electrocardiogram shows nonspecific repolarization abnormalities. Your initial impression is that the patient is suffering from anxiety and you recommend that no further cardiac testing is necessary. After discussing this with your patient you are asked: "Doctor, should I stop drinking coffee? What can caffeine do to my heart?" How would you approach these questions?*

## INTRODUCTION

The association between coffee and the risk of cardiovascular (CV) disease, particularly arrhythmias, has been a topic of research for the past 20 years. However, the conclusions of the published studies have been diverse. Even though caffeine is widely consumed, to date there have been no randomized, controlled trials with adequate statistical power analyzing the direct relationship between caffeine intake and CV risk factors or adverse events. It is important to note that caffeine has been the primary focus of most coffee-consumption studies (O'Keefe et al., 2013), yet it is merely one of hundreds of compounds present in coffee. Our limited knowledge of the relationship between caffeine intake and adverse CV events is based on case reports, retrospective studies, and small physiologic trials with only short-term follow-up that cannot be generalized to all populations. Surveys conclude that most physicians recommend that patients with known heart disease avoid or reduce their caffeine intake, yet strong evidence to support this advice is lacking (Hage & Iskandrian, 2012; Pelchovitz & Goldberger, 2011).

## THE BASICS

Caffeine is a methylxanthine alkaloid derivative (Corti et al., 2002; Frost & Vestergaard, 2005; Glatter, Myers, & Chiamvimonvat, 2012; Hage & Iskandrian, 2012; Mattioli, Farinetti, Miloro, Pedrazzi, & Mattioli, 2011; O'Keefe et al., 2013; Pelchovitz & Goldberger, 2011) present in coffee, chocolate, certain teas, sodas, and some commonly used over-the-counter drugs. In 150 ml of coffee, for example, there are approximately 80 to 100 mg of caffeine (Pelchovitz & Goldberger, 2011). According to the Food and Drug

Administration, intake of up to 400 mg of caffeine per day is considered safe (U.S. Food and Drug Administration, 2013). At low or moderate doses (less than 100 mg, or 100–200 mg, respectively), caffeine acts as a nonspecific competitive antagonist of adenosine receptors, inhibits the phosphodiesterase enzyme, and increases cytosolic calcium concentrations, therefore triggering or enhancing cardiac conduction and activity (Hage & Iskandrian, 2012; Kinugawa, Kurita, Nohara, & Smith, 2011). According to laboratory data, caffeine also acts as a sympathomimetic by stimulating the release of catecholamines, which results in vasoconstriction (Frost & Vestergaard, 2005; Mostofsky, Rice, Levitan, & Mittleman, 2012). Immediately after consumption, caffeine affects certain chemoreceptors in the gastrointestinal tract, indirectly causing increased heart rate, cardiac output, and blood pressure to enhance flow to the splanchnic vasculature (Pelchovitz & Goldberger, 2011).

## THE PROS AND CONS

Many studies have revealed undesirable effects of caffeine on the CV system, namely the development of arrhythmias, hypertension, and even heart failure (Birkett & Logan, 1988; Frisoli, Schmieder, Grodzicki, & Messerli, 2011; Mattioli et al., 2011). An increase in systolic blood pressure several minutes to hours after intravenous administration has been demonstrated in animal models in the lab (Bohn, Ward, Hodgson, & Croft, 2012; Corti et al., 2002; Frisoli et al., 2011; McMullen, Whitehouse, Shine, Whitton, & Towell, 2011). Additionally, exacerbation of atrial arrhythmias has been observed in humans after oral consumption (Kinugawa et al., 2011; Parasramka & Dufresne, 2012; Pelchovitz &

Table 1 | Effects of Coffee on Cardiovascular Health

Blood Pressure	Transient elevation acutely in nonhabitual drinkers; no effect (tolerance) with regular intake
Insulin Sensitivity	Increase in adiponectin levels; decrease in insulin resistance from upregulated IGF-1 signaling
Serum Lipids	Increase in total and LDL cholesterol (with boiled coffee, not filtered)
HS CRP	Decrease
Arrhythmias	No association between consumption and incidence of supraventricular arrhythmias, or frequency or severity of ventricular arrhythmias
Congestive Heart Failure	Decrease in risk with four cups per day; increase in risk with fewer than or more than four cups per day (U-shaped curve, not statistically significant)
Coronary Heart Disease	Decrease in risk with moderate consumption (one to two cups per day)
Mortality	Decrease in risk of cardiovascular mortality in patients without preexisting cardiovascular disease (dose-response protective effects)

Goldberger, 2011). Based on the observations made by Kinugawa et al., the effect of caffeine on atrial rhythms is more pronounced when high doses are administered to subjects who might be caffeine sensitive (Kinugawa et al., 2011). It is important to note, however, that these hypotheses are based on limited observations, that the acute effects of caffeine administration tend to resolve within several hours, and that tolerance to caffeine's effects readily develops when caffeine is regularly consumed. Because of these observations, the long-term effects of caffeine consumption on blood pressure and arrhythmias are not considered clinically significant; however, prospective randomized studies to evaluate the longitudinal effects of caffeine have not been conducted (Corti et al., 2002; McMullen et al., 2011; Pelchovitz & Goldberger, 2011). A random survey in 1988 of more than 2,000 patients concluded that there was no statistically significant evidence that habitual caffeine intake increased the risk of hypertension (Birkett & Logan, 1988).

In a canine model, the degree and severity of arrhythmias secondary to caffeine administration were found to be dose-related. In small clinical studies, moderate coffee consumption was associated with atrial fibrillation persistence, particularly in hypertensive patients (Kinugawa et al., 2011; Mattioli et al., 2011). After analyzing a case of atrial tachycardia exacerbated by caffeine and after reviewing other caffeine-related arrhythmia cases, Kinugawa concluded that in certain patients, moderate caffeine consumption can produce QRS interval prolongation and shorten effective refractory period of the right atrium, the atrio-ventricular node, and the right ventricle, which may be associated with significant atrial and ventricular arrhythmias (Kinugawa et al., 2011). However, case reports cannot always demonstrate causality, and the possibility that these patients might be particularly sensitive to caffeine due to baseline conduction abnormalities cannot be ruled out.

Table 1 summarizes the effects of coffee consumption on cardiovascular health, which are well described by O'Keefe

et al. (2013). Klatsky, Hasan, Armstrong, Udaltsova, and Morton (2011) found that moderate caffeine intake was inversely related to the risk of hospitalization due to arrhythmias, suggesting that it is highly unlikely that caffeine ingestion increases arrhythmia risk. The consumption of 4 cups of coffee per day had a moderate but statistically significant inverse relationship with heart-failure incidence, yet, as the consumption per day increased, the association had no statistical significance (the so-called J-curve relationship) (Mostofsky et al., 2012). A cohort from the Danish Diet, Cancer, and Health Study did not discover an association between the amount of caffeine consumed per day and the risk of atrial fibrillation or flutter (Frost & Vestergaard, 2005). This study had the strength of a large sample size, given the high coffee consumption and prevalence of atrial fibrillation in Denmark. It is important to note that these studies are observational and subject to behavioral bias.

Most epidemiological data related to caffeine consumers suggest that moderate coffee intake is not associated with CV disease and might even have protective effects (Hage & Iskandrian, 2012). Studies have suggested that caffeine metabolites may even have positive effects on endothelial function, glucose metabolism, cholesterol transport, oxidative stress, and platelet function, among other processes (Bohn et al., 2012; Mattioli et al., 2011). Caffeine may reduce atherosclerosis via several active compounds that function as potent antioxidants, which can reduce reactive nitrogen species, protect against apoptosis, and even reduce oxygen consumption in vascular smooth muscle (Mercer, Gray, Figg, Kumar, & Bennett, 2012).

#### THE BOTTOM LINE . . .

The available literature suggests that caffeine consumption is generally safe, but reports of its indirect effects on the cardiovascular system must not be completely disregarded. These findings should prompt us to educate patients about the possible acute effects of moderate to high caffeine doses in nonhabitual consumers and advise patients with

preexisting cardiovascular disease to consume with caution until the medical community has a clear understanding of caffeine's direct relationship with CV disease.

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