Caffeine and atrial fibrillation: friends or foes?

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INTRODUCTION

Caffeine is a methylxanthine compound that has pleiotropic cardiovascular effects, including stimulation of the sympathetic nervous system. Caffeine is ingested daily by a large percentage of the global population (in the form of tea, coffee and cola), and is the most widely consumed vasoactive substance in the world.[1]

The relationship of caffeine to cardiovascular disease has been debated and investigated for decades. Considered a stimulant, caffeine had long been postulated to be proarrhythmic. Initial physiologic measurements in humans showed that acute caffeine ingestion in caffeine naïve subjects increased heart rate and blood pressure, and correlated with increases in plasma renin and catecholamine levels.[2] Electrophysiological studies performed in the 1980s during acute caffeine loading (both oral and intravenous) demonstrated a heterogeneous pattern of effect in cardiac tissue, with caffeine prolonging the myocardial refractory period in the left atrium and shortening the refractory period in the right atrium.[3] In these experiments, patients seemed to have an increased proclivity to develop supraventricular arrhythmia after caffeine loading.

The results of these early studies suggested a deleterious effect of caffeine on cardiovascular health. Importantly, however, these studies investigated the acute effects of caffeine ingestion and not the chronic effects of daily exposure in a habituated subject. The keen interest in identifying potential ill effects of caffeine consumption led to high-profile publications, including one linking coffee drinking to pancreatic cancer—a finding later debunked, as it resulted from the use of flawed statistical and study design methods.[4]

Recently, interest in identifying risk factors for supraventricular arrhythmias has increased—particularly with respect to atrial fibrillation (AF), given the high prevalence of this dysrhythmia and the risk of stroke that its presence confers. Subsequently, a number of large observational cohort studies have failed to show any association between caffeine intake and AF.[5 6] In this issue of Heart, Caldeira and colleagues present results from their meta-analysis of studies examining the association of chronic caffeine ingestion and AF in order to better define that relationship.[7]

Study results and limitations

Using standard search methodology, Caldeira and coinvestigators compiled a list of studies eligible for inclusion in their meta-analysis. Studies of patients with no prior history of AF who had adequate follow-up (≥6 months) were targeted. A total of seven studies were included in the final analysis. A total of 116 000 patients (mean ages 51–62) were studied. The mean follow-up in the studies was highly variable, ranging from 4–25 years.

Some of the included studies only reported caffeine use through coffee, while others took into account all types of caffeinated beverages. The authors took each study and defined caffeine non-consumers as the group with the lowest reported exposure—in some studies, this represented true non-consumers of caffeine, but in the others it represented the bottom quintile of caffeine consumption. For each study, the lowest reported exposure group was used as the reference and the remainder of the patients were pooled in order to calculate an OR associated with caffeine use for developing AF. Given the regional variations in coffee preparation, estimates of the caffeine content of coffee in any given study were based on the geographic location of the population studied.

The authors found that there was no significant association between caffeine exposure and incident AF (OR 0.92; 95% CI 0.82 to 1.04; $p>0.05$). When studies of lower quality were excluded, they found that the odds for developing AF was significantly lower in caffeine consumers (OR 0.87; 95% CI 0.80 to 0.94; $p<0.05$). In a prespecified analysis, the authors found that subjects with low-dose caffeine intake had a lower risk for AF than those with zero caffeine intake (OR 0.85; 95% CI 0.78 to 0.92; $p<0.05$). This subgroup analysis showed that moderate and high users of caffeine did not derive a benefit with regard to AF compared with caffeine non-users.

A number of limitations to the study exist and need to be acknowledged. There are problems inherent with meta-analysis when the designs of the included studies' designs are radically different, as was the case here. Specifically, there was substantial variation in the way that caffeine consumption data was collected and in the determination of the outcome of AF (ranging from direct evaluation of ECG to the use of administrative coding data). One of the included manuscripts was not primarily designed to quantify caffeine use and did not specify how caffeine consumption data was collected.[8] A few of the studies did not report fully adjusted point estimates. At face value, there were large disparities in the studies' designs and statistical analyses; not surprisingly, this is borne out by the I^2 statistic, which indicated significant heterogeneity in the reported results. Overall, when the quality and consistency of the included studies is in question, the results of a meta-analysis must be interpreted with caution.

To the authors' credit, they did perform a sensitivity analysis with the lower quality studies excluded. The authors found a protective effect of caffeine consumption with regard to incident AF, but it is important to note that this sensitivity analysis was not prespecified. The study heterogeneity was reduced in this subanalysis (I^2 dropped from 72% to 39%), though the meaning of this statistic when applied to such a small number of studies is not clear.

Challenging classic teachings

Over the years, anecdotal reports have fostered the notion that caffeine can cause AF.[9] As a known stimulant, this association has been deemed biologically plausible. What is often forgotten, however, is that published case reports invariably involve the acute ingestion of very large quantities of caffeine (often with concomitant alcohol use), as are contained in today's energy drinks. As a result, the notion that caffeine ingestion is proarrhythmic had become 'common knowledge'. This assumption carried implications for clinical care, including the widespread practice of withholding caffeinated beverages from patients in coronary care units. More recently, however, the pendulum has swung in the other direction. Large-scale observational studies such as the Framingham cohort and Women's

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Health Study have shown no significant association between chronic caffeine ingestion and AF.[5 6] Canine studies showed that the infusion of caffeine actually lowers the window of vulnerability to AF.[10] One well-executed observational study even suggests that habitual coffee consumption is protective against cardiovascular disease.[11]

Caldeira and colleagues provide us with further evidence that caffeine ingestion does not confer an increased risk of developing AF. Given the quality and heterogeneity of the studies included in the meta-analysis, however, it would be a stretch to take the results of the subanalyses and conclude that caffeine is actually protective against AF.

Next steps

Caldeira and colleagues help to advance the discussion about how caffeine affects cardiovascular health, specifically the risk of arrhythmia. However, there remain many questions. Are the associations reported here spurious? Do they represent a cardioprotective effect of caffeine, or do they represent a cardioprotective effect of some other chemical contained in coffee? Might the vehicle of caffeine delivery be a critical part of this effect? In short, there continues to be equipoise as to whether caffeine ingestion is beneficial to health.

What is needed to help sort this out is a randomised controlled trial of some easily normalisable form of caffeine (ie, pills). However, the potential for de facto crossover due to non-study–related caffeine consumption is high and the task of conducting such a trial over the long periods of time necessary to achieve an adequate number of endpoints is daunting. At present, we can at least reasonably conclude that low-moderate levels of caffeine consumption are safe with regard to cardiac arrhythmia. However, given the proliferation of energy drinks that contain massive quantities of caffeine and other stimulants, it is important to temper any message that suggests that caffeine is beneficial. Particularly in the paediatric population, there remain concerns that binge consumption of these energy drinks can cause serious arrhythmias.[12] With respect to cardiac dysrhythmias, caffeine used in moderation does not appear to be a foe, but the jury is still out on whether it is truly a friend.

Contributors PDB is the primary author of the Editorial Comment. KH provided important input with regards to the content and editing of the manuscript.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Bhave PD, Hoffmayer K. *Heart* 2013;**99**:1377–1378.

► http://dx.doi.org/10.1136/heartjnl-2013-303950

Heart 2013;**99**:1377–1378.
doi:10.1136/heartjnl-2013-304543

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Heart

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Heart 2013 99: 1377-1378
doi: 10.1136/heartjnl-2013-304543