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Caffeine's Effects on Propagating Arrhythmias

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Abstract

Caffeine, for various reasons, has often been associated and even blamed for certain conditions and problems. In particular, caffeine is commonly associated by doctors with cardiac arrhythmia and atrial fibrillation because of its vasodilation and stimulant properties, among other effects. Belief that these properties incite and even worsen the heart conditions has prompted doctors to advise patients to refrain from caffeine consumption. This is difficult considering the wide use of the chemical throughout the beverage world. A common additive, caffeine is found in everything from coffee to sodas, with a wide range of concentrations. To completely abstain from the drug would require large amounts of patience, knowledge of what is safe to drink, and self-control. However, there is a debate over whether this is actually necessary. Some research and doctors have come forward, questioning the restriction of the chemical and the presuppositions behind the restriction. Those questions have in turn led to a multi-sided debate on caffeine and how it affects heart conditions, specifically, cardiac arrhythmia and atrial fibrillation. In order to form a conclusion, different literature about the subject including a variety of studies was reviewed. The different epidemiological, human, animal, and population studies and reports determined the answer to be one of four things: caffeine is an arrhythmogenic, caffeine is not an arrhythmogenic, caffeine inhibits arrhythmias, or there is not enough research. Ultimately, the conclusion was insufficient reliable research to make any sound conclusion. Caffeine should be taken with caution or avoided entirely by those at-risk for arrhythmias. There is a lack of coordinated research on all sides for all the studies, including epidemiological, human, and population. Conducting research in a coherent manner should bring forward more reliable and consistent results, allowing a strong conclusion to be made.

Keywords: Caffeine, Arrhythmisa, Cardic

1. Introduction

Perhaps the most prevalent of all drugs in use throughout the U.S. is caffeine. Its uses for awareness and energy among other traits make it a versatile additive to any number of beverages and foods. However, the health effects are still in question, especially its effects on the heart. As it is, a small yet significant portion of the population of the United States suffers from various forms of cardiac disease, including arrhythmias and atrial fibrillations. These are potentially fatal conditions and when active, these problems can cause increased heart rate, irregular beats, and sometimes heart failure. Because of the vaso-dilatory characteristics of caffeine, and suppositions that it aggravates arrhythmias, doctors have historically advised patients with cardiac disease to restrict consumption of the chemical.

But is this the correct assumption? Does the research show a direct link between caffeine consumption and aggravation of cardiac arrhythmia? If it does, then doctors must warn their patients of something that could potentially harm them. If it doesn't, then doctors need to stop the restriction of caffeine solely for cardiac reasons as it limits the consumer from a product they may enjoy and causes them unnecessary troubles in avoiding the substance. Due to its pervasive use throughout the beverage world, complete avoidance means no end of difficulty and frustration in formulating a diet.

Many doctors and scientists have researched this topic in various ways, some for restriction of caffeine, and others against its restriction. Different methods of tests have included epidemiological and population studies, human and animal tests, and case reports. All of these give valuable insight into the debate and the evidence for each side but the research appears to differ in areas and thus, the different sides of the debate. The debate is multisided with the different viewpoints categorized into one of three groups, with all groups calling for more comprehensive research and tests while still claiming an answer. The predominant view holds that caffeine must be restricted with patients who have cardiac arrhythmias or atrial fibrillation. Those of this opinion hold that the research does show a direct correlation between caffeine use and an increase in cardiac arrhythmia and atrial fibrillation attacks. Their opposites deny this. The research, they hold, does not give any reason to believe that caffeine effects cardiac arrhythmias in any way. The third party, a small but strengthening minority, state that research has actually come out to promote caffeine use. The claim is that caffeine inhibits cardiac arrhythmias and atrial fibrillation and that this is supported in many examples of research.

The debate is ongoing and somewhat confusing. Although some literature exists that compares the different sides and show one as more reliable, they are suspect because of uncontrolled variables, unaddressed issues and potential bias. Because of these oversights, wild variables and bias, the literature demands an unbiased review to provide a clearer picture from which the debate can be decided. There are problems with some of the research on both sides and gaps that need to be filled including insufficient testing in certain areas. After taking into account the lack in some research and problems with others, I believe that no successful conclusion can be made about caffeine and its effects on arrhythmia. Caffeine should be taken with extreme caution and moderation by those at risk for arrhythmias and atrial fibrillation.

2. Background

Perhaps the most prevalent and widely used legal drug in the United States is caffeine, and one of the most convenient drugs for recreational use. Mentioned in Chou and Benowitz (1994), caffeine holds the record as the most used stimulant in the world, with 75% taken in beverage form. Fifty-five different countries produced approximately six million tons each year, forty five million pounds of it Americans consume annually and at an increasing rate, most commonly in the form of coffee, an extremely popular beverage worldwide (p. 173). While Americans do not drink as much as other nations, most notably Sweden and Finland, 53% of Americans consumed it as of 1991. This number does not include any number of other caffeinated beverages also consumed whole sale including caffeinated sodas, teas, and energy drinks. Combined together, Americans consumed daily on average 200 mg of caffeine in 1991, with heavy users ingesting as much as 1 gram or more a day (p. 174). Another report cited in a study by Dobmeyer et al. (1983) reported the consumption at 10^9 kilogram of coffee a year (p. 814). As Glatter, Myers, Chiamvimonvat, (2012) notes, caffeine is the most commonly consumed vasoactive substance in the world.

This constant use of caffeine is guaranteed by its physiological and chemical properties. With its ability to increase energy levels and vigilance in the consumer, caffeine is a common energy booster, making it a useful additive to energy drinks. However, perhaps the real reason for its constant use is its addictive effects. One study, Griffiths and Woodson (1988), cited in Chou and Benowitz reported an increase in coffee consumption as the caffeine content per cup decreased. Habitual use reinforces the practice, promoting caffeine consumption in the consumer. Chou and Benowitz also noted that caffeine can cause a “vicious reinforcing cycle” for smokers as it was found that smoking increased as caffeine ingestion decreased. In addition, quitting the substance is inhibited by withdrawal symptoms in the form of headache, fatigue, and rarely anxiety, impaired psychomotor skills, and craving for coffee (p. 177).

More concerning for cardiologists is the effects of caffeine on the interactions in and around the heart. Caffeine inhibits receptors for adenosine and actively prevents the effects of that same chemical. In so doing, caffeine interferes with the adenosine receptors which help in cardiovascular regulation. Phosphodiesterase cannot act as effectively in the presence of caffeine, though not at the low levels previously thought (Chou and Benowitz, p. 176) (Glatter et al., p. 530). These are among the most serious characteristics of caffeine that prompt many doctors to restrict its use by patients, especially those at risk for heart conditions.

Heart conditions most associated with caffeine use are the cardiac arrhythmias. Arrhythmia, and atrial fibrillation, are disorders of the heart where the heart beats too fast (tachycardia), too slow (brachycardia), or irregularly with atrial fibrillation. Death can occur in extreme cases of these disorders. A statistical report compiled by Lloyd-Jones et al. (2010) in concert with the Center for Disease Control (CDC) reported 36,860 confirmed mortalities and 461,016 reported mortalities from cardiac arrhythmia. The report mentioned a total of 835,000 patients hospitalized for the condition in 2010 alone (p. e91). This is the total for all arrhythmias including atrial fibrillation according to

the report. These numbers, while small compared to overall population, are significant nonetheless and they continue to grow. From 1996 to 2001, the number of people hospitalized for atrial fibrillation alone rose by 34% (p. e91). In response to this, and with suppositions of caffeine's involvement, many doctors recommended abstinence from caffeine to patients with arrhythmias. The American Heart Association wrote in their online recommendations that caffeine be prohibited in any diet for those with cardiac arrhythmias, (AHA website).

3. Arguments for Restriction

Despite the disagreement and questions, many doctors still hold that caffeine is an arrhythmogenic in that it propagates arrhythmias. Multiple studies, two of which are discussed here, support their statements, showing links between caffeine and cardiac arrhythmias. An experiment conducted by Dobmeyer, Stine, Leier, Greenberg, and Schaal (1983) explored the electrophysiological effects of caffeine in nineteen volunteer patients with a control of seven normal, healthy adults. Conduction, intervals, and signals were all measured 100 to 150 beats a minute through atrial pacing. The patients were diagnosed with arrhythmia when the event happened for thirty seconds or more. The caffeine was ingested orally and injected intravenously, 200 mg for each in 200 mL doses. Of the patients, 12 of the 19 had a previous record of cardiac arrhythmia and/or atrial fibrillation (p.814). Dobmeyer et al. diagnosed arrhythmia when it lasted longer than thirty seconds.

A total of four people contracted arrhythmia, two momentarily, one for four beats, and the last for 70 beats at a rate of 270 beats per minutes (p.815). An additional three others of the control experienced an atrial flutter after the caffeine ingestion. Only one person had arrhythmia before the caffeine injection. Before the caffeine, one out of the twelve patients had tachycardia and six others suffered attacks afterwards. From the other test results, sinoatrial, interartrial, atrioventricular-node, and Purkinje conduction intervals did not change as a result of caffeine ingestion. However, the refractory period of the right side of the heart significantly decreased while the refractory period of the left ventricle increased (p.815). The authors conclude from this experiment that caffeine does increase arrhythmia attacks in those who are already at risk for arrhythmias. The fact that some patients of both the control and the experimental groups contracted arrhythmia attack after caffeine ingestion suggests arrhythmogenic properties in caffeine and that it is a hazard to those with arrhythmias.

A few reservations exist towards this study. There are very few volunteers actually tested on in this experiment with only a total of nineteen patients. Since the sample is so small results are devalued as a smaller test group means it is less likely to represent the population as a whole. Those patients may be more or less susceptible to caffeine than others and therefore the study would not yield generalizable results. In addition, the amount of caffeine used was equal to that of an entire day's worth of caffeine concentrated into one dose (Chou and Benowitz, p. 174), (Dobmeyer et al., p. 814). The results then are not indicative of an average intake of coffee in one sitting and should not be seen as totally suggestive of caffeine's effects. One more reservation relates to the age of the study. Some of the results may be due to older equipment which may misread due to the inefficiency of such systems as outside sources could skew the readings or even some readings not even noticed. Reproducing this experiment with modern equipment and receiving the same results could reaffirm the results of this experiment.

The study by Dobmeyer et al. is not the only experiment to suggest that caffeine is an arrhythmogenic. Donnerstein et al. (2005) conducted a different experiment with similar results. The doctors performed this test on twelve different patients, six men and six women in order to more accurately determine the physiological effects on the different genders. None had any history of heart problems and all had abstained from caffeine intake forty-eight hours in advance of the test (p. 643). The volunteers split into different equal groups, control and experimental. Depending upon the group, patients received either four ounces of fruit punch spiked with caffeine or a placebo consisting of just fruit punch. Patients would drink a total 5 mg/kg body weight of caffeine. Electrocardiograms tests were administered before and after ingestion for comparison of results. At the hypothetical peak of caffeination, ninety minutes after ingestion, the control and the experimental groups switched drinks, with the control taking the caffeine laced fruit punch and the experimental taking the placebo. The differences in the electrocardiogram tests were found by overlaying the graphs on a computer system.

The results displayed an interesting trend. The test showed that patients' heart rates and atrial conduction remained unchanged throughout the experiment. With the placebo, the P-wave and QRS complex did not alter at all for the entire duration of the experiment (p. 644). After caffeine ingestion, nine of the eleven patients experienced prolonged QRS complexes after ninety minutes and eight out of nine patients after three hours (p. 644). Ectopy, P-wave duration, and heart rate did not change at all ninety or 180 minutes after caffeine consumption. While the results were not seen as clinically significant because of the size of the change, they do have importance. Since only

a small amount of caffeine was used, the results are statistically significant and should be viewed with concern and researched more. The authors conclude from this experiment that while small amounts of caffeine are not problematic, moderate to large dosages should be avoided with those who have heart conduction issues, specifically atrial fibrillation and cardiac arrhythmia.

The study conducted by Donnerstein et al. suffers from similar issues as the Dobmeyer et al. study. Most notable is the sample size of the experiment. A small number of patient/volunteers participated, leaving the results with the same sense of unreliability that appears in the Dobmeyer et al. study. In addition, there was no accounting for the effects of the fruit punch on the caffeine or digestion of it. While it sounds unfounded, the author consider it an unknown variable as there is no knowing with the given evidence whether it amplifies or limits the effects of caffeine.

Several other studies and experiments, many of them animal studies and case reports, have shown caffeine as an arrhythmogenic substance. A study by Belle et al. in which caffeine was directly injected into dogs found that caffeine lowers the amount of energy necessary to activate ventricular fibrillation (Pelchovitz and Goldberger, p. 285). Other animal studies did show signs of cardiac problems, including arrhythmias. However, these were accompanied by large dosages of caffeine and, in some cases, norepinephrine and propranolol (p. 285). Propranolol is a beta-blocker and could possibly prevent or severely limit the effects of caffeine, skewing the results. These and other studies showed an arrhythmic effect of caffeine but others do not. Also, since these are animal studies, the results should not be applied to humans as there are a number of physiological differences, including body size, metabolic mechanisms.

While the evidence is there to restrict caffeine consumption in those with arrhythmias, it is based on studies with small test sizes and some unaccounted variables. Animal studies, while useful in determining the effects of caffeinated substances without harming humans, cannot be directly applied to humans because of physiological differences. Until these differences are taken into account, a safe conclusion cannot be built on them. Therefore, the situation requires more research to form a conclusion.

4. Non-Restriction of Caffeine

While the movement for caffeine restriction is prevalent, indicated by the American Heart Association's advisory to patients to abstain, doctors have come forward questioning that stance based on new evidence. Rather than stating that caffeine is an arrhythmogenic, the doctors hold that caffeine does not affect arrhythmias at all. They do recognize that it may have other properties that are potentially harmful but do not cause or worsen arrhythmias.

A surprising number of articles have appeared stating a non-arrhythmogenic link between caffeine and arrhythmias. One meta-analysis by David J. Pelchovitz and Jeffrey J. Goldberger (2011) goes into detail analyzing studies that suggest a link between caffeine and arrhythmia as well as those that show no such connection. Through review of a number of case studies, experiments and epidemiological studies, they formed a conclusion. They first analyzed some human studies for implications. In a Japanese study, caffeine barely affected serum concentrations in men, with a minimal increase of cholesterol. The difference between those who drank none and those who drank 7 cups or more was only 13 mg/dL. Other studies showed similar negligible results in other areas, 250 mg of caffeine did nothing to exercise duration and increased blood pressure by only 7 mmHg. In addition, the blood pressure effects are minimalized in habitual caffeine users due to tolerance build-up (p. 285). This suggests that a tolerance can be built up for the effects of caffeine, decreasing the possibility that the drug increases problems.

Furthermore, larger studies were conducted furthering the idea that caffeine has no effects in promoting arrhythmias. A study performed on 45,589 patients by Grobbee et al. (1990) showed no increased risk for atrial fibrillation or cardiac arrhythmia. Things get more uncertain with electrocardiogram tests, such as the aforementioned Donnerstein et al. study. The experiment results showed an increase in only the QRS duration with nothing else affected. This increase is statistically significant but was considered 'likely' insignificant by the authors as it was a small change (p. 285). The same group, Donnerstein et al., later conducted an additional test with 400 mg of caffeine that found no change in any electrocardiogram parameters except for heart rate. This suggests a minimal effect, if any, by caffeine.

Animal studies were more consistent with their results and allow more leeway in what can be done. The experimenters often use large dosages of caffeine in these experiments, amounts that would be considered unethical in human experiments (p. 285). An experiment conducted by Belle et al. found that caffeine reduces the threshold for ventricular fibrillation after injecting 12.5 mg/kg into dogs. Other experiments found dose dependent effect of caffeine on tachycardia initiation. Ventricular tachycardia and atrial fibrillations exist only at high dosages. A study

conducted on dogs found no connection between arrhythmia and caffeine, with none of the test subjects contracting arrhythmia.

Human epidemiological studies have shown some connection between caffeine and arrhythmia. One test found that premature ventricular contraction was increased with caffeine ingestion in males who drank more than nine cups of coffee daily. A few studies failed to find any connection between caffeine and arrhythmias, with no increase of arrhythmias or atrial fibrillations found in the subjects. The authors conclude that moderate caffeine use does not increase the chances for arrhythmia or atrial fibrillations. The epidemiological studies support this and the animal studies cannot be applied to human due to physiological differences.

The authors raise valid points in this analysis, discussing the various problems with experiments and showing how the same group obtained different results on two similar tests. They also claim that the results in the first mentioned Donnerstein et al. experiment was not significant. Animal studies are also brushed aside. These stances are not wholly acceptable and should be reconsidered. Although the Donnerstein et al. group obtained dissimilar results from two similar experiments, that should not be a call for tossing out the results but instead investigating the methods or applying more tests. Also, though the results for the first test were clinically insignificant, statistically they hold some weight because of the small amounts of caffeine used. As for the animal studies, those kind of experiments are a major way of drug and medicine testing for pharmaceutical companies as well as more private experiments. Results are trusted and used to show how a substance will affect humans. The authors should not simply brush aside the results because of physiological differences but instead explain in detail why they are not applicable.

Another meta-analysis came to the same conclusion as the Pelchovitz and Goldberger report. In this study, Chou and Benowitz (1994) review different experiments and studies conducted previously. They did this in response to the massive amounts of caffeine consumed annually in the U.S. While some effects of caffeine are relatively easy to show, some chronic symptoms are difficult to substantiate or agree on, especially those concerning the heart. Much of the research that addresses caffeine's cardiovascular effects are contradictory or inconclusive and are old, some from the early 1900's (p. 178). Several studies, Lang et al., 1983; Robert- son et al., 1978, 1984, 1981, discussed in the meta-analysis show that caffeine alters the blood pressure and heart rate in doses greater than or equal to 5 mg/kg. As cited in the paper, a study conducted by Robertson et al. (1978) found that at those dosages the heart slows for an hour after and then increases two to three hours after. However, tolerance quickly builds up to these responses, showing that caffeine has little overall effect on blood pressure and heart rate. With prolonged use, caffeine can establish some more permanent effects on the blood pressure, but they are small and barely affect the user.

As for arrhythmias, which many believe to be linked to caffeine, Pelchovitz and Goldberger hold that little literature supports the idea. While in massive amounts it can alter the ventricular fibrillation threshold and increase the chance for arrhythmia, such amounts are rarely consumed. While Prineas et al. did show in their experiment that those who drank nine cups or more of coffee would suffer premature beats such connection was weak and not significant (p. 185). Multiple studies mentioned in the article show no link between caffeine and arrhythmias. They either showed no change in any monitored body function or showed results small enough to be accounted insignificant. Chou and Benowitz conclude that caffeine should not be restricted from patients solely for preventing arrhythmia as the literature does not support such an idea.

This conclusion is not the best one. The research is insufficient for any such conclusion as there are no follow up experiments, duplication of experiments, or even mention of how conflicting experiment results came to be. Rather than state that the literature does not support the restriction of caffeine, a safer conclusion would be to call for more research as the current amount is inconclusive.

5. Caffeine as Potentially Beneficial

For most of the debate, the question was over whether caffeine does or does not affect arrhythmia and by extension whether it should be restricted from those with arrhythmias. Now a new side has emerged. Evidence has come forward suggesting an inhibitory effect of caffeine on arrhythmias and adding another voice to the ongoing discussion. While by far the smallest of the sides in terms of supporting research, it is growing as more research is conducted.

A meta-analysis written by the aforementioned Glatter, Myers, and Chiamvimonvat (2012) claims that caffeine does nothing to promote cardiac arrhythmias. The article suggests a possible inhibitory effect of caffeine. Two epidemiological studies specifically showed an inverse relation between caffeine consumption. An Italian study

looking at 11,323 patients' post-MI found such results with those who drank less coffee appearing to be at a higher risk for coronary heart disease, stroke, and arrhythmias than those who drank more coffee (p. 531). The Stockholm Heart Epidemiology Program (SHEEP) received similar trends in their study with those drinking more than seven cups of coffee a day having a lower death rate than others (p. 531). While these studies are contradicted by others, the results are still there. Based on the research Glatter, Myers, and Chiamvimonvat claim that only when ingested in abnormally large amounts will caffeine have effects on the heart and that most of its vasoactive properties are neutralized by natural bodily functions. In addition, caffeine may yet have a positive effect in which it slows or inhibits the occurrence of arrhythmia. They further proposed that more research is necessary as the current amount is inconclusive.

While the sources provided show an inverse relation between caffeine and arrhythmia, it is just two mentioned out of many studies. As noted in the analysis, there are other studies that contradict these results and may just be anomalies. Furthermore, the research they represent stating that caffeine does not promote arrhythmias lack commentary on research that does suggest caffeine as an arrhythmogenic. This oversight and lack of research supports the authors call for more research as nothing can be concluded without a wealth of raw information and in depth analysis of the research.

There is more research that supports the idea that caffeine inhibits arrhythmias. Arthur L Klatsky, Amul S Hasan, Mary Anne Armstrong, Natalia Udaltsova, and Cynthia Morton (2011) conducted an epidemiological experiment on 130,054 patients to study the relation between caffeine and arrhythmia. The study included 3,137 patients previously hospitalized for cardiac arrhythmia, and an additional 1,200 patients known to have arrhythmia. A cox proportional hazards model with 8 covariates explained the results in terms of the coffee-related risk in 3137 persons hospitalized for cardiac arrhythmia. At yearly checkups, patients were examined for arrhythmia and were questioned as to their daily caffeine intake as well as ethnicity, age, gender, other demographics and medical history (p. 20). Answers were multiple choice and included 'seldom to none, one or less, one to three, and four or more'. Questions about other beverages that include caffeine, such as tea and sodas, also appeared in the questionnaire. Doctors questioned 9.3% of patients according to the type of coffee they drank. After observation, their hospitalization/death records were reviewed. The results showed little to no correlation between caffeine consumption and arrhythmia. In fact, there appeared to be an inhibiting effect of caffeine on cardiac arrhythmia, where those who drank caffeinated beverages were less likely to suffer from arrhythmias. The hazard ratio decreased for those who drank more coffee a day, from .97 with less than one cup for any arrhythmia to .82 for four or more cups of coffee daily, statistical evidence suggesting an inverse relation (p. 22). However, the authors were careful to point out potential problems of the study.

There are some unknowns for this experiment, some of them mentioned by the authors themselves. First and foremost, the potential of misunderstanding the questionnaire as well as forgetting information could throw the results. As with all epidemiological studies there is always that hazard of patient error where they lie, misunderstand, or do not remember correctly the questions and answers. Obviously, this could skew the results. Because of this epidemiological studies must be viewed with caution and the results of this experiment treated appropriately.

One additional study found similar results to the previous study. Grobbee, Rimm, Giovannucci, Colditz, and Stampfer (1990) conducted a study on 51,529 men ranging 40 to 75 years old (p. 1026). The volunteers answered questions concerning their ethnicity, medical history, and diet for the previous year as well as frequency of drinking coffee. The average weight and content of caffeinated beverages was calculated using a specified portion multiplied by weight to frequency of use ratio. The authors calculated the hazard ratio associated with caffeinated and non-caffeinated coffees. The results showed only a small connection between increased cardiovascular and increased caffeinated coffee consumption while increased ingestion of decaffeinated coffee correlated with increased cardiovascular disease (p. 1030). However, the authors were not expecting any increase in cardiovascular disease in those who drank four or more cups a day and declared that more research was needed (p. 1031).

This experiment is designed to fully understand the relation between the diet and cardiovascular disease. However, it runs into problems. Grobbee et al. place much of the experiment in the hands of the volunteers who must answer the questions as accurately as possible as well as constantly and consistently monitor their food intake. This leaves the results open to multiple errors. The unexpected results found in the experiment may very well be a consequence of these potential errors.

6. Conclusion

After reviewing the given literature and evaluating the different methods, results, and analyses the author concludes that there is not enough coordinated and coherent research to show arrhythmogenic effects in caffeine or lack thereof. Those at risk for arrhythmias and cardiovascular disease should treat caffeine with caution. The literature supporting the belief that caffeine promotes arrhythmia is filled with experiments that although show a link, demonstrate a link that is weak. The sample sizes of the studies are small, often not exceeding twenty patients. In addition, much of their support comes from animal tests which may or may not be applicable to humans. Furthermore, research is not repeated to confirm previous results potentially leaving avoidable mistakes in as given evidence. Doctors and researchers should clarify this and conduct more coordinated studies. No safe conclusion can be made and doctors should advise patients to treat caffeine cautiously.

While there is much to be said for the lack of restriction of caffeine, that side too has issues that need to be addressed. They do not give adequate response and explanation of why some evidence should be used and others shouldn't. In a few instances they brush aside some evidence by stating that it was contradicted by other information. This is does not mean that the evidence should be disregarded. This indicates inconclusive results which calls for more research into these areas. The studies also lack follow up and repeat experimentation to validate results.

Finally, the studies indicating caffeine's role in inhibiting arrhythmias lacks in supporting research overall. Much of their evidence comes from epidemiological studies that are open to errors in many areas which devalues the overall argument. Little to no clinical studies exist supporting the claim and no animal study reviewed suggest any inhibitory effects of caffeine on arrhythmias. This must be rectified in order to give credibility to this argument.

Altogether, all sides need to coordinate research, studies, and experimentations in order to reach a conclusion most can agree with. Previous studies should be reviewed and attempts made to replicate results using similar methods. In some cases, oversights and experimentation variables should be corrected to protect against error. Studies that give contradicting results should be scrutinized and their methods investigated. Rather than dismissing out of hand results that disagree with others, researchers need to look into why those results appeared. Until the research is done, and a definitive answer is given on the effects of caffeine, doctors should advise patients at risk for heart disease and arrhythmias to avoid caffeinated beverages out of basic caution over a substance with unknown effects.

7. References

American Heart Association (2013). "Tachycardia, fast heart rate". May 2, 2013. May 30, 2013. http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Tachycardia-Fast-Heart-Rate_UCM_302018_Article.jsp

Chou, Tony M., Benowitz, Neal L. (1994) "Caffeine and coffee: effects on health and cardiovascular disease". *Comparative Biochemistry and Physiology*. vol. 109, no. 2, pp. 173-189. Doi: http://dx.doi.org/10.1016/0742-8413(94)00048-F

Diedrick E. Grobbee, Eric B. Rimm, Edward Giovannucci, Graham Colditz, Meir Stampfer. (1990). "Coffee, caffeine, and cardiovascular disease in men." *The New England Journal of Medicine*. 323:1026-1032. Doi: 10.1056/NEJM199010113231504

Dobmeyer, David J, Stine, Ronald A., Leier, Carl V., Greenberg, Richard, and Schaal, Stephen F. (1983). "The arrhythmogenic effects of caffeine in human beings." *New England Journal of Medicine*. 308. 814-816. Retrieved from: http://www.nejm.org/doi/full/10.1056/NEJM198304073081405

Donnerstein, Richard L., Zhu, David, Samson, Ricardo, Bender, Alyse M., Goldberg, Stanley J. (1998) "Acute effects of caffeine ingestion on signal-averaged electrocardiograms". *American Heart Journal*. 136(4) 643-646 Doi: http://dx.doi.org/10.1016/S0002-8703(98)70011-0

Glatter, Kathryn A., Myers, Richards, Chiamvimonvat, Nipavan. (2012). "Recommendations regarding dietary intake and caffeine and alcohol consumption in patients with cardiac arrhythmias: what do you tell your patients to do or not to do?" National *Institute of Health*. 14(5). 529-535. Doi: 10.1007/s11936-012-0193-6

Klatsky, Arthur L., Hasan, Amul S., Armstrong, Mary Anne, Udaltsova, Natalia, and Morton, Cynthia. (2011) "Coffee, caffeine, and risk of hospitalization for arrhythmias." *The Permanent Journal*. 15(3): 19–25 as given in http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3200095/

Lloyd-Jones D, Adams RJ, Brown TM, et al. (2009). “Heart disease and stroke statistics - 2010 update.” *Journal of American Heart Association*. 121:e1-4, 11 and e91 Doi: 10.1161/CIRCULATIONAHA.109.192667
Pelchovitz, Daniel J., Goldberger, Jeffrey J. (2011) “Caffeine and cardiac arrhythmias: a review of the evidence”. *The American Journal of Medicine*. 124(4) 284-289 Doi: http://dx.doi.org/10.1016/j.amjmed.2010.10.017