The effect of caffeine consumption on blood pressure: Habitual versus naïve consumers.

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Abstract

Caffeine is consumed on a massive scale worldwide. Some of the major immediate effects of caffeine which have been described in the literature include increased blood pressure and the stiffening blood vessels. Other work has shown that habituated caffeine consumers do not experience these effects to the same extent as naive consumers. We continued to investigate the effect of caffeine on blood pressure, as well as pulse wave velocity in caffeine-habituated and caffeine-naive consumers. We gave doses of caffeine to caffeine- habituated university students (n=10) and caffeine-naive university students (n=10). Blood pressure was recorded using an automatic blood pressure cuff and wave pulse velocity was calculated using an electrocardiogram (ECG) setup and finger pulse transducer. Pulse wave velocity did not change in habitual consumers or naive consumers after caffeine consumption (p-value= 0.090, p-value= 0.863). However, changes in systolic blood pressure after caffeine consumption were different between the two groups (p-value= 0.036); a greater increase was found habituated consumers. The change in diastolic blood pressure change was the same (p-value= 1.000) and change in mean pulse wave velocity was the same (p-value= 0.645) between caffeine-habituated and caffeine-naive consumers. Caffeine had different pressor effects on caffeine-habituated and caffeine-naive consumers, with a significant difference in the systolic blood pressure change in these groups. However, caffeine had similar effects on diastolic blood pressure and pulse wave velocity of the two groups.

Introduction

Caffeine, is the world's most popular psychoactive substance and is found naturally in the beans, leaves and fruit of over 60 plants. It is consumed daily by people all over the world in coffee, tea, cola soft drinks, energy drinks and chocolate. Many people consume it due to its best-known effect, temporarily warding off drowsiness. Caffeine is a xanthine alkaloid compound that acts as a central nervous system and metabolic stimulant (Nehlig et al. 1992). It is used both recreationally and medically

to reduce physical fatigue and restore mental alertness when weakness or drowsiness occurs. After ingestion, Caffeine is completely absorbed by the stomach and small intestine within 45 minutes and is then distributed throughout all tissues of the body. Caffeine is metabolized in the liver by the cytochrome P450 1A2 oxidase enzyme and broken down into three primary metabolic dimethylxanthines: paraxanthine (84%), theobromine (12%), and theophylline (4%) (Ferre & O'Brien, 2011). Paraxanthine increases lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma, theobromine dilates blood vessels and increases urine volume, and theophylline relaxes the smooth muscles of the bronchi.

Because the caffeine molecule is both water-soluble and lipid-soluble, it readily crosses the blood–brain barrier that separates the bloodstream from the interior of the brain. Once inside the brain, the principal mode of action of caffeine is as an antagonist of adenosine (A1 or A2A) receptors (Fisone et al. 2004). The caffeine molecule is structurally similar to adenosine and binds to adenosine receptors, acting as a competitive inhibitor. This effect, interrupts adenosine that normally serves to inhibit the release of many neurotransmitters, such as noradrenaline, dopamine, acetylcholine, glutamate and GABA. The result is an increase in the levels of epinephrine and norepinephrine/noradrenaline released via the hypothalamic-pituitary-adrenal axis (Bertil et al. 1999). Epinephrine, the natural endocrine response to a perceived threat, stimulates the sympathetic nervous system, leading to increases in heart rate, blood pressure and blood flow to muscles.

Vlachopoulos et al. (2003) examined the effect of a caffeine dose on aortic elastic properties and arterial wave reflection in 20 healthy subjects. They found caffeine to increase systolic and diastolic blood pressures in response to caffeine. They also found that radial and aortic pulse pressures, and pulse wave velocity increased significantly in response to caffeine. The proposed mechanisms for sustained increases in pulse wave velocity do not just involve passive changes (blood pressure), but also intrinsic properties of the aorta. Vlachopoulos and colleagues (2003) concluded, caffeine has a

vasoconstrictive effect via antagonism of endogenous adenosine or increased circulating catecholamines.

Although caffeine consumption can have contrasting effects, causing vasodilation and vasoconstriction, it is the acute phenomena of vasoconstriction that leads to increased blood pressure (Nurminen *et al*. 1999). This pressor effect is well documented, Nurminen *et al* compiled many studies showing that a 200mg dose of caffeine is capable of raising the systolic blood pressure of normotensive individuals by 3-14 mmHg. This effect has also been noted to be increased in individuals who do not normally consume caffeine when compared to those who do. Therefore, caffeine's effect on blood pressure has been found to be dependent on habituation (Zimmerman-Viehoff *et al.* 2016). This study will examine how caffeine affects the blood pressure and wave pulse times of habitual and naïve coffee consumers, and then compare the differential responses of the two groups. We hypothesize that after caffeine ingestion, blood pressure will have a greater increase in naïve consumers versus habitual consumers. Therefore, wave pulse times will decrease more in naive consumers than in habitual consumers.

Methods

For our experiment a total of twenty healthy university students (18-26 years old) were selected to participate in this experiment. Of the twenty subjects, 10 were deemed habitual caffeine consumers and 10 naive caffeine consumers. We defined habitual caffeine consumers as individuals who consume the equivalent of 4 mg or more of caffeine per kilogram of body weight daily, and naive consumers as those who only consume 1 mg or less of caffeine per kilogram of body weight daily (Baron and Roberts 1996). Subjects were not separated into groups based on race or sex, as caffeine has been found to have similar effects on blood pressure between those groups (Myers *et al*. 1988. Strickland *et al*. 1989. Bak and Grobbee. 1994. James. 1994).

Every potential subject was given a questionnaire prior to coming into the lab, which was used to determine personal caffeine intake and age. Body weight was determined by measurement from a scale measuring in kilograms. We excluded individuals with a history of heart issues from the study to mitigate any possible risk of someone having a negative reaction to the caffeine tablets. While the scientific community mostly agrees that there is no relationship between caffeine and conditions like myocardial infarctions, some older studies suggest that there may be a link (Curatolo and Robertson. 1983).

For every subject both pulse wave velocity and blood pressure were measured before and after caffeine consumption. Wave pulse time was measured using a PowerLab setup including a finger pulse transducer and electrocardiogram (ECG) setup with shielded lead wires, each measurement lasted 30 seconds. Five wave pulse times were taken from each subject by using the marker and cursor in labchart to measure from the R peak of the ECG to the peak of the finger pulse transducer signal. The mean of these five values was taken for data analysis. It is important to note that the peak of the finger pulse transducer signal does not represent the moment the wave pulse reaches the finger. Rather the bottom of the peak, where the signal begins to rise is the actual moment the wave pulse arrives, but for ease of measurement we will be measuring from the peak. Blood pressure was measured using an automatic blood pressure cuff (life source model).

The PowerLab setup consisted of a PowerLab data acquisition unit that was connected to a lab computer with LabChart software. A bio amp cable was connected to the data acquisition unit. Earth, CH1 NEG, and POS shielded lead wires were connected to the Bio Amp cable. Before attaching disposable electrodes to each subject's left iliac crest and clavicle areas, the skin in these areas were abraded with abrasive gel to reduce resistance then cleaned with an alcohol swab to remove dead skin cells. Once the disposable electrodes were attached, the earth (green) shielded lead wire was attached to the electrode on the left clavicle, the Channel 1 negative (white) shielded lead wire was attached to

the electrode on the right clavicle, and the Channel 1 positive (black) shielded lead wire was attached to the electrode on the left iliac crest. A finger pulse transducer was connected to input 2 on the powerlab and the pad was placed on the tip of the left index finger.

Prior to testing, participants were instructed to avoid caffeine consumption in the 24 hours leading up the test. The half-life of caffeine in plasma ranges from 3 to 7.5 hours (Curatolo and Robertson. 1983), therefore, essentially all caffeine was eliminated from participants bodies prior to testing.

Once a participant entered the lab they were allowed to rest for 5 minutes in a comfortable chair. First the baseline blood pressure and wave pulse times were recorded. After this, the subjects were given their caffeine dose. The doses were slightly dependent on subject weight, the caffeine dose was not fully customized to each subject's body weight as we could only administer portions of half a pill (200mg Allmax caffeine tablets); 100 mg (½ tablet) was administered for every 50 kg of the subject's body weight. Subject body weight was rounded to the nearest 50 kg for dose (example, weight 84.4kg, 200g dose). Once the subject ingested their dose of caffeine, they were allowed to leave the lab for 60 minutes, this allowed for the maximum absorption of the caffeine. Once the subject returned to the lab, they were once again instructed to rest for 5 minutes, before blood pressure and wave pulse times were measured again for comparison to the baseline measurements.

The data was statistically analyzed using paired t-tests to see if there is a statistical significant difference between the blood pressures and pulse wave times within the two experimental groups. Further paired t-tests were also used to see if the difference in blood pressure and mean wave pulse before and after caffeine was different between the groups. All tests were run using a confidence level of 95%. Data for systolic and diastolic blood pressure was represented by a single measured value. Data for wave pulse was represented as the mean of 5 values taken from each subject.

Results

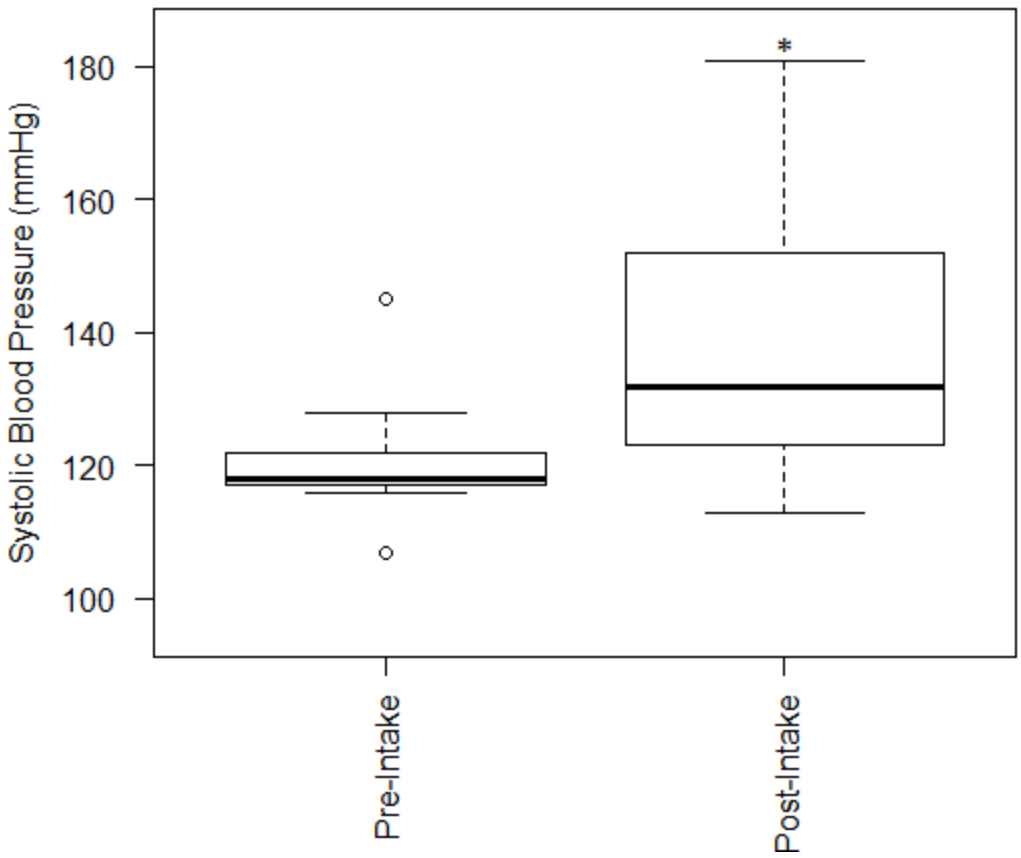


Figure 1. Systolic blood pressure of habitual caffeine consumers (n=10), before and after caffeine consumption.

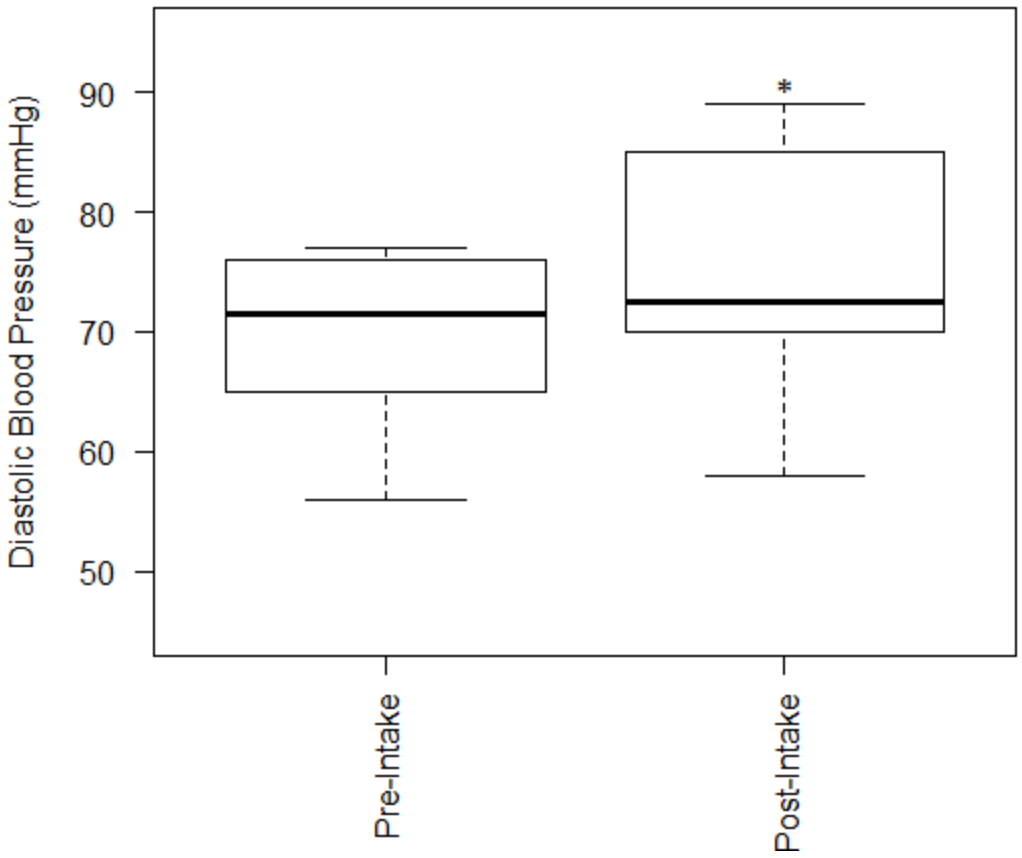


Figure 2. Diastolic blood pressure of habitual caffeine consumers (n=10), before and after caffeine consumption.

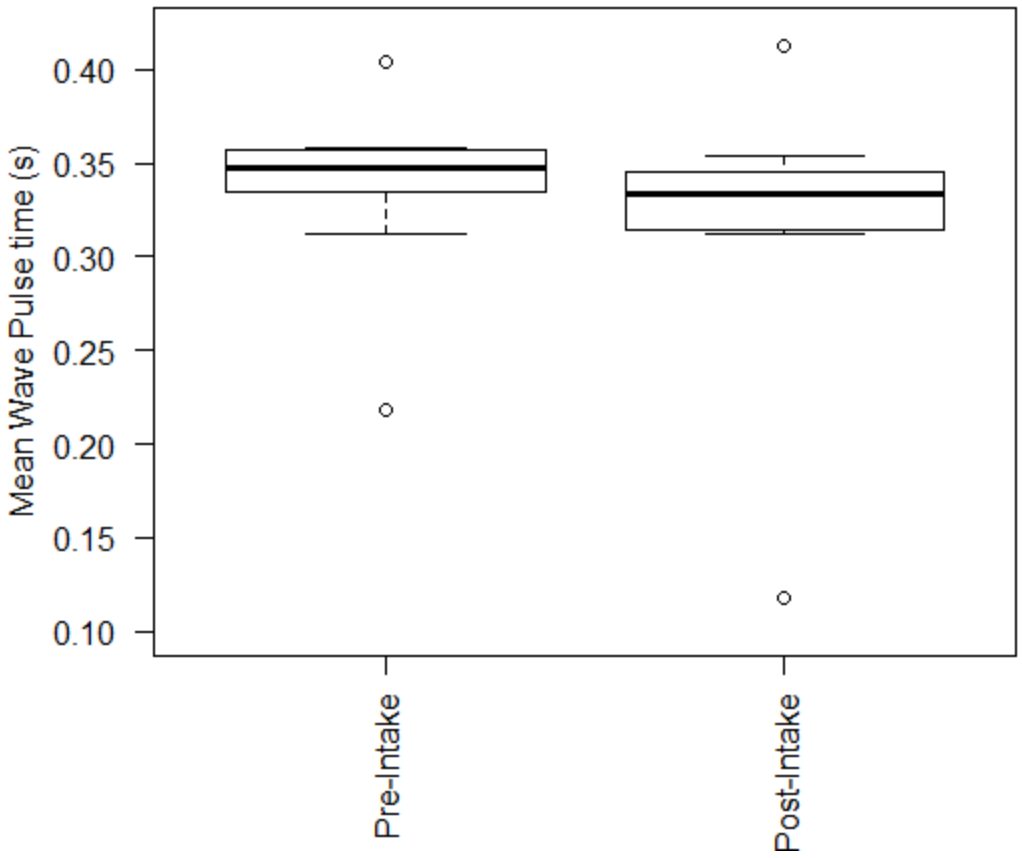


Figure 3. Mean wave pulse time (s) of habitual caffeine consumer (n=10), before and after caffeine intake.

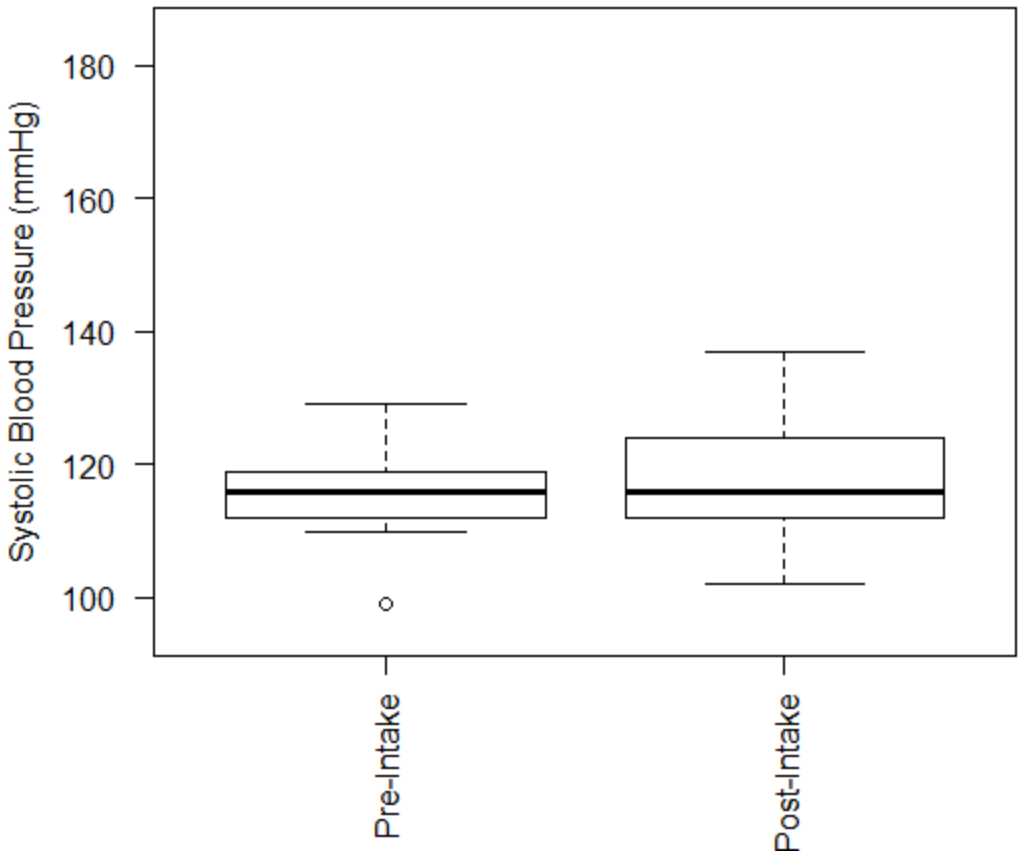


Figure 4. Systolic blood pressure of naive caffeine consumers (n=10), before and after caffeine consumption.

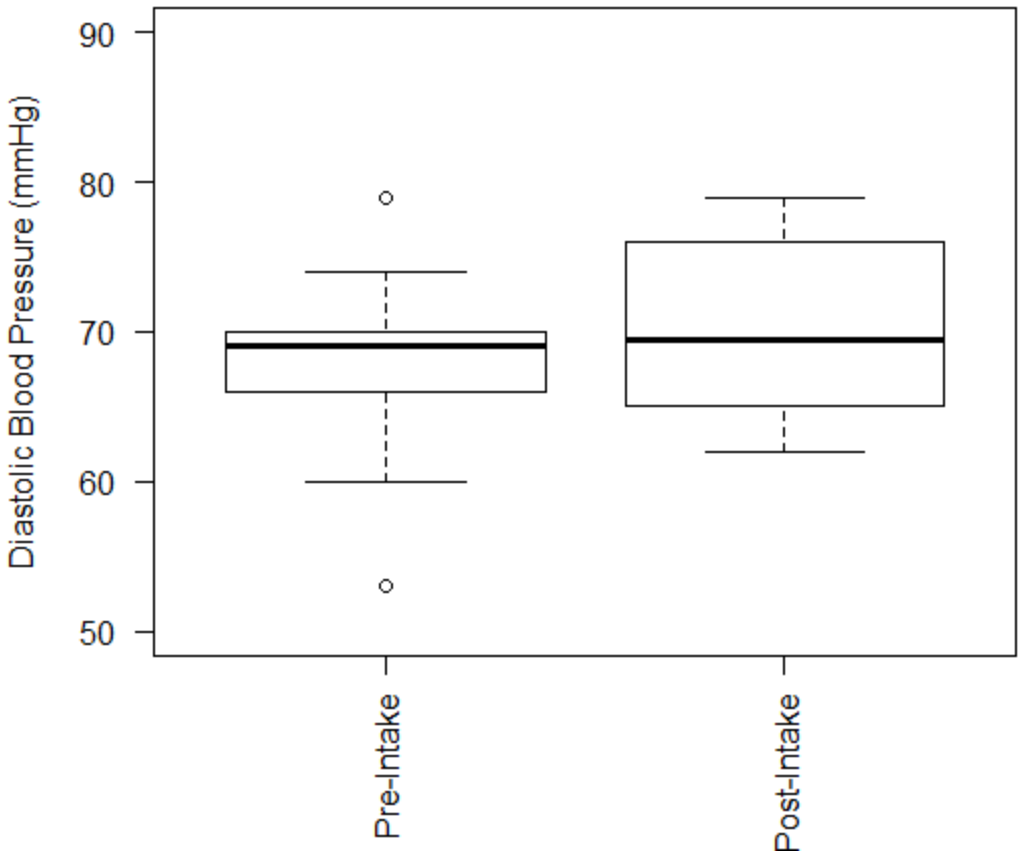


Figure 5. Diastolic blood pressure of naïve consumers (n=10), before and after caffeine consumption.

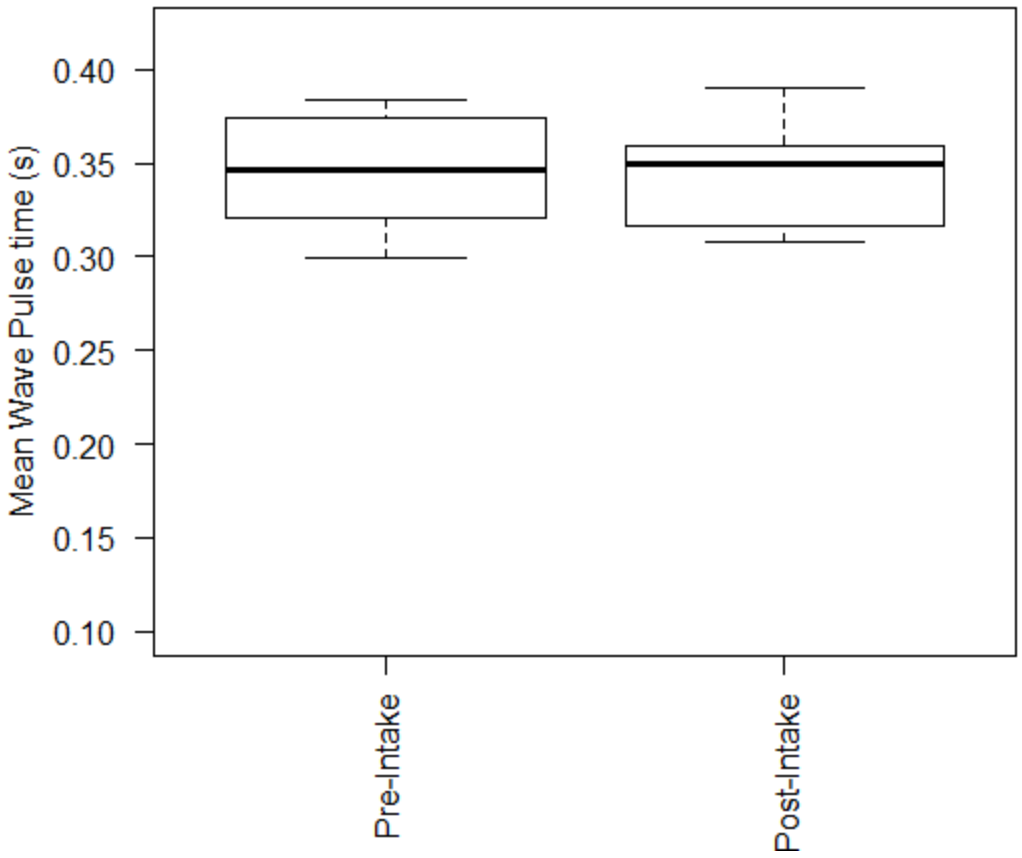


Figure 6. Mean wave pulse time (s) of naive caffeine consumer (n=10), before and after caffeine intake.

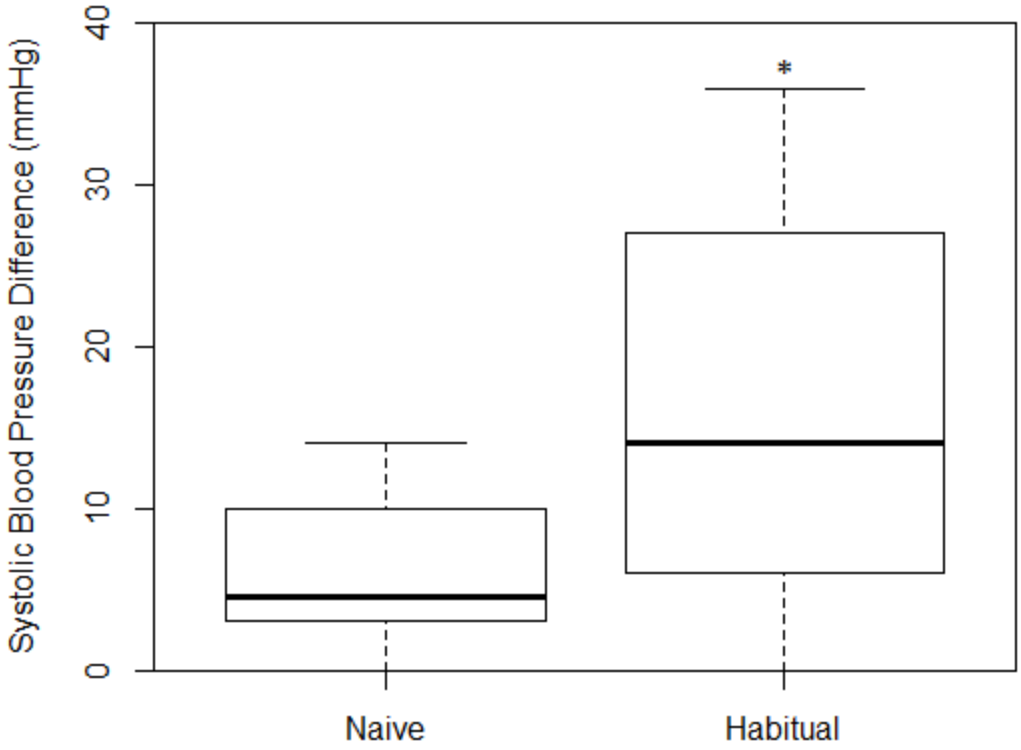


Figure 7. Comparison of the difference in systolic blood pressure before and after caffeine intake between naive and habitual caffeine consumers (n=20).

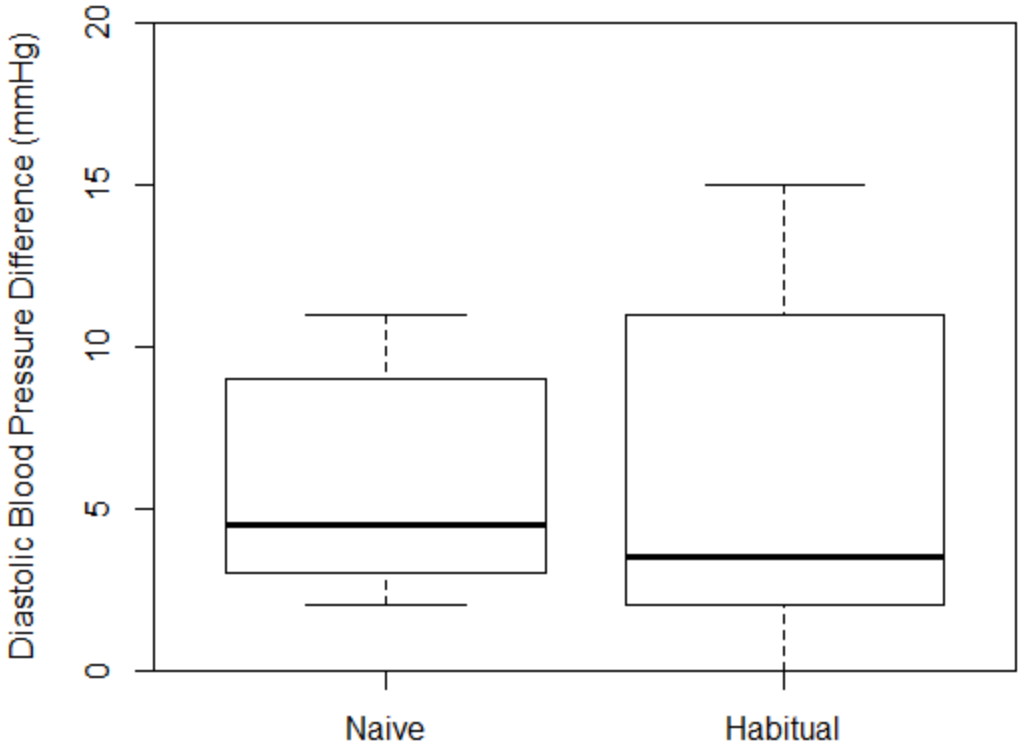


Figure 8. Comparison of the difference in diastolic blood pressure before and after caffeine intake between naive and habitual caffeine consumers (n=20).

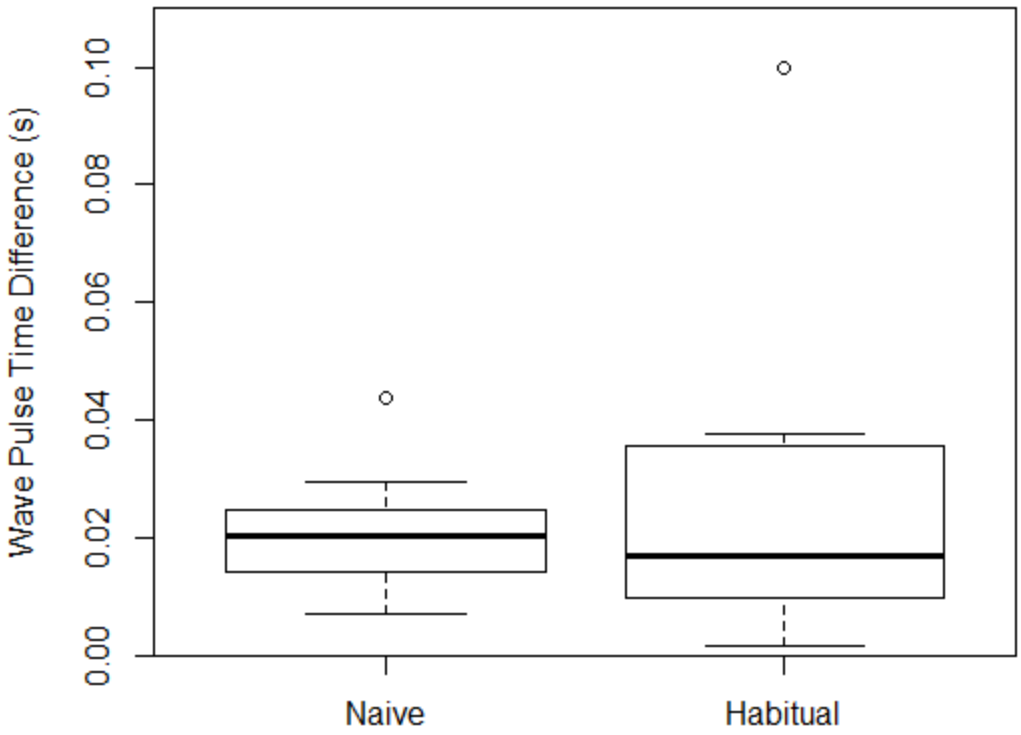


Figure 9. Comparison of the difference in mean wave pulse times before and after caffeine intake between naive and habitual caffeine consumers (n=20).

To begin our analysis, we started by looking at the change in our monitored variables within our experimental groups. This was done to establish if any change was even occurring within the experimental groups, before comparing data between the groups. In habitual consumers systolic blood pressure after caffeine consumption was found to be significantly higher than systolic blood pressure before caffeine (p-value= 0.03 < α=0.05) (Figure 1.). Habitual consumers also showed statistically significant difference in diastolic blood pressures before and after caffeine consumption (p-value= 0.025 < α=0.05) (Figure 2.), with diastolic blood pressure trending higher after caffeine consumption. Even

though the previous two variables differed before and after caffeine consumption in habitual consumers, mean wave pulse did not (p-value= 0.090 > α=0.05) (Figure 3.). For naive consumers we found that there was no difference in systolic blood pressure (p-value= 0.513 > α=0.05) (Figure 4.) or diastolic blood pressure (p-value= 0.205 > α=0.05) (Figure 5.) before and after caffeine consumption. Additionally, no difference was found in the mean wave pulse time for naive consumers before and after caffeine (p-value= 0.863 > α=0.05) (Figure 6.).

The actual hypothesis of this experiment addressed the question of the differential blood pressure response of habitual and naive consumers after caffeine consumption. When we looked at the values obtained for the difference in systolic blood pressure before and after caffeine intake in habitual and naive consumers we found that there was a statistically significant difference between the groups (p-value= 0.036 < α=0.05) (Figure 7.). This test showed that habitual caffeine consumers saw a larger increase in systolic blood pressure when compared to naive caffeine consumers. That difference was not maintained in diastolic blood pressure, where we found no difference in the diastolic blood pressure response to caffeine in habitual and naive caffeine consumers (p-value= 1.000 > α=0.05) (Figure 8.). Additionally, there was no difference in the change in mean wave pulse time between habitual and naive consumers (p-value= 0.645 > α=0.05) (Figure 9.).

Discussion

The primary findings of this study showed that habitual caffeine consumers experienced a larger increase in systolic blood pressure after caffeine consumption when compared to naive caffeine consumers (Figure 7.). Additionally, we found no difference in the changes of diastolic blood pressure and mean wave pulse times in response to caffeine between habitual and naive consumers (Figure 8, Figure 9.). Supporting analysis also showed that habitual caffeine consumers had significantly higher systolic and diastolic blood pressures after caffeine consumption (Figure 1, Figure 2.), while naive

consumers showed no statistically significant change in these variables (Figure 4, and Figure 5). Our analysis on wave pulse shed no light on our results either as we found no difference in mean wave pulse time before and after caffeine in both habitual and naive caffeine consumers (Figure 3, Figure 6). Our hypothesis included the prediction that that after caffeine ingestion, blood pressure will have a greater increase in naïve consumers over habitual consumers. So, the analysis does not only disagree with our hypothesis, but our data actually acts in the opposite direction of what we were expecting. Our hypothesis was based on previous peer-reviewed articles, so it follows that our hypothesis should be true. This discussion will focus on the possible reasons our data did not follow the expected outcome. Possible explanations could include experimental error, and other bodily mechanisms acting as counter-effects to the effect of caffeine.

Farag et al. (2010) examined the pressor effect of caffeine in 165 healthy men and women that were separated into six groups based on their sex, age and hormonal status. They saw significant increases in systolic blood pressure in all their groups and saw significant increases in diastolic blood pressure in all groups except in young men. In the current experiment, only young individuals were tested (aged 19-26); so, if caffeine does not affect the diastolic blood pressure of young men, the results of our current study would have been impacted. Farag et al. (2010) also found that caffeine induces a significant pressor response even in habituated individuals, contrary to common belief. This supports the results of the current study in that there were no significant differences between habitual and naïve caffeine consumers, except the result of a significant increase of systolic blood pressure after caffeine consumption seen in habituated consumers.

Kennedy et al. (2008) examined the effect of a “normal cup of coffee” on the cardiovascular and mental alertness response in 10 caffeine-naïve and 10 caffeine-habituated females. They monitored blood pressure, heart rate, and mental alertness before and after coffee intake. The primary finding of this study was that caffeine-naïve participants had increases in both systolic and diastolic blood pressure

after coffee intake, while caffeine-habituated participants only had an increase in diastolic blood pressure. This result is reflective of what was expected to happen in the current experiment. It is important to note that the results of their study also showed a significant decrease in diastolic blood pressure of caffeine-naïve and caffeine-habituated individuals when participants were subject to both coffee and mental stress. Therefore, stress may have had an impact on the results of the current study, since only university students, who are often under great stress, were tested.

Stress and age are both involuntary and unavoidable factors when testing university students. However, the voluntary action of smoking, that many young adults take part in, has also been described to have an effect on caffeine breakdown. Caffeine metabolism is known to be accelerated in cigarette smokers (Brown et al. 1988). In a study done by Grela et al. (2013) they found that tobacco smoke does in fact increase the elimination rate or caffeine rate as well as its two metabolites: theophylline and paraxanthine. However, pharmacokinetic parameters for theobromine did not differ after exposure to tobacco smoke which suggested that tobacco smoke does not alter the elimination rate of theobromine. In a different study done by De Leon et al. (2003), they reported that smokers had lower plasma caffeine concentration than non-smokers which also supports the conclusion that tobacco smoke increases caffeine metabolism. We did not ask if potential subjects were smokers on our questionnaire, as we were unaware of the effects. So, it is possible this may have also a contributed to the results of our study, and inadvertently affected the outcome of the experiment.

Another possibility for the opposing results received could be the result of genetics, there is growing evidence that individual differences in caffeine response or caffeine consumption are related to genetic factors. Genetic factors may influence responses to caffeine directly, by altering acute or chronic reactions to the drug, or indirectly, by affecting other psychological or physiological processes that are related to the drug effect.

There are three levels of sensitivity to caffeine. These levels determine how well individuals metabolize caffeine and to what degree its stimulating properties affect them. The three classes include: Hypersensitivity, normal sensitivity, and hyposensitivity. Individuals who have normal sensitivity to caffeine can usually have 200-400 mg of caffeine daily without any adverse reactions. Individuals who are hypersensitive to caffeine will react to very small amounts of the substance. For these people, it can take nearly twice as long for caffeine to metabolize. On the opposite end of the spectrum are those who are hyposensitive to caffeine, they make up about 10% of the human population. They process caffeine so efficiently that they may take large doses (>500 mg) without much effect at all.

Caffeine sensitivity is determined by the efficiency of the human body to process and metabolize caffeine. Caffeine is metabolized by the liver using the enzyme CYP1A2 (cytochrome P450). This enzyme accounts for about 95% of caffeine metabolism and shows wide variability of activity between persons (Cornelis et al. 2007). The ability to produce this enzyme is regulated by the CYP1A2 gene. Therefore, slight changes in the DNA sequence for the CYP1A2 gene have a significant impact on its efficiency and thus greatly determine the rate of caffeine metabolism for the individual (Renda et al. 2012). Replacement of the A nucleotide with a C nucleotide in the rs762551 region within the CYP1A2 gene results in reduced enzyme activity. Individuals carrying two copies of the C allele at rs762551 of this gene are more sensitive to caffeine than those carrying two copies of the A variant (Rogerio et al. 2018). Therefore, carriers of the C allele can be considered slow caffeine metabolizers, and carriers of the A allele can be considered rapid caffeine metabolizers (Cornelis et al. 2007).

Another gene influencing caffeine sensitivity is the AHR (aryl-hydrocarbon receptor) gene. This gene encodes a protein that regulates the amount of CYP1A2 in the body, by controlling when and how the CYP1A2 gene is switched on and off. When AHR detects xenobiotics in the body and induces transcription of CYP1A2. With the production of CYP1A2, the body is then able to metabolize the ingested caffeine. It was found that people who consume over 400 mg of caffeine, the equivalent of 4

cups of coffee, per day are more likely to be carriers of a variant of the AHR gene (C allele of the single nucleotide polymorphism rs4410790). About 49% of the general population carries the C allele of AHR. Scientists believe that the C allele increases the AHR protein's activity in switching CYP1A2 on (Renda et al. 2012), therefore allowing for rapid caffeine metabolism. This would result in a hyposensitivity to caffeine where the ingested dose would have little to no effects on the individual.

It was mentioned in the introduction that caffeine functions through adenosine A_1 and A_{2a} receptors on the cell surface; these two receptors have partially opposing effects. Animal studies have shown that chronic intake of caffeine increases the density of A_1 receptors, which are believed to be responsible for caffeine tolerance (Shi et al. 1993). In contrast, a variation in the gene ADORA2A, encoding for A2a, is associated with sensitivity to caffeine. Specifically, individuals carrying two copies of the C allele at rs5751876 of this gene are more sensitive to caffeine than those carrying two copies of the T allele (Yang et al. 2010). Those with the T allele are more likely to experience anxiety after consuming caffeine. It is entirely possible that the aforementioned genetic factors could have had a significant effect on our results.

A final possible reason for our results may be due to caffeine and theobromine's differential effects on blood pressure. In a study conducted by Mitchell et al. (2011), they tested the effects of solo caffeine, solo theobromine, and caffeine + theobromine on mood and blood pressure. They concluded that when tested alone, theobromine, a component of caffeine, actually caused vasodilation, lowering blood pressure. When caffeine and theobromine were tested together they found no significant effect on blood pressure. Proposing that the contrasting effects canceled one another out. Another study conducted by Dutch scientists, found that with the addition of theobromine to cocoa, central blood pressure significantly decreased when compared to the placebo of regular cocoa (Van Den Bogaard et al. 2010). Theobromine itself causes vasodilation and does this by inhibiting phosphodiesterase (Van Den Bogaard et al. 2010). The inhibition of phosphodiesterase causes an accumulation of cyclic adenosine

monophosphate (cAMP), as the phosphodiesterase is responsible for its breakdown. This accumulation of cAMP leads to vasodilation (Echeverri et al. 2010). Since caffeine is broken down into metabolites that cause their own effects on the body before being further broken down, it is possible that the theobromine component peaked in the blood plasma at the same time that the initial vasoconstriction from the caffeine was taking place. This is turn would cancel each other's effects out, and therefore, cause no significant difference in pre and post caffeine blood pressures in the participants.

A limitation to this study is the dosage of caffeine. We customized the doses, so participants consumed approximately 100 mg of caffeine per 50 kg of body weight, for comparison most studies use doses equivalent to 200-300 mg of caffeine. However, doses smaller than 200 mg have been seen to cause pressor responses (Kennedy et al., 2008). Additionally, our study was only able to monitor blood pressures at two points, once before caffeine intake and once after. We might have gotten different results if we were able to monitor blood pressure continuously over and for longer periods of hours rather than only 60 minutes. We cannot properly generalize the findings of this study to a larger population because our sample size was relatively small and there are a wide variety of variables that need to be taken into account when considering the effects of caffeine including genetics, stress and smoking status.

In summary, we did not see what we expected in our expected results. This difference in our study compared to others may have been the result of poor experimental design, experimental error, or possibly factors beyond our control, including differential caffeine sensitivity, and genetic variability. Future experiments on this topic should include a larger and more diverse sample size to better represent the population. They should also take continuous recordings over time periods of hours. Lastly, future studies should also design their experiments more carefully in order to account for variables such as stress, smoking status or sensitivity levels to caffeine.

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