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Ischemia and reperfusion with and without caffeine

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Abstract

We have been investigating selected effects of caffeine on the cardiovascular system of young adults for the past several years [1-4]. The young adults have been enrolled in courses such as Systems Physiology (01:146:346), Systems Physiology Laboratory (01:146:357), and Advanced Physiology (01:146:456) at Rutgers University. We selected young adults because there has been little effort by the medical/scientific communities to investigate their cardiovascular health; and, because there should be little doubt that the cardiovascular health of young adults is changing in the current obesity/overweight pandemic (circa post-1990). We have found that caffeine increases peripheral vascular resistance (1-4) and markedly reduces peripheral blood flow [1-4]. Caffeine also attenuates reactive hyperemia [2] and pressure-flow autoregulation [3].

The current experiment is a follow up to examine caffeine's effects on the peripheral circulation of the toes. After four minutes of zero-flow occlusion, reperfusion (reactive hyperemia) was monitored for sixteen minutes. In all students reactive hyperemia was markedly and significantly reduced by caffeine, reflecting attenuation of the regulation of pedal arterial blood supply. These results are consistent with our prior experiments and demonstrate the potentially harmful effects of caffeine on the cardiovascular system of young adults.

Keywords: ***Caffeine; Pedal artery; Peripheral ischemia; Reperfusion; Blood flow***

1. Introduction

Consumption of coffee in the United States has reached a two-decades (all time) high according to information recently released by the National Coffee Association (NCA). Sixty-six per cent of Americans drink coffee each day, more than any other beverage including tap water according to the NCA. That number has increased by fourteen per cent since January 2021, the

single largest increase since NCA began tracking data. Additionally, about eighty-four per cent of those who drink coffee have had the substance at home in the past day (compared to eighty per cent in January 2020) [5].

For those addicted to chemical substances including coffee, there is usually a 'drug of choice' (e.g., alcohol, cocaine, heroin, marijuana, tobacco). For America's adult population that specific chemical seems to be caffeine. It has been estimated by various sources that 80-90 per cent of the adult populations of industrialized nations such as the U.S. and E.U. consume caffeine on a daily and regular basis [6-8]. Because little medical or scientific attention has been given to this pandemic no one seems to care. Moreover, all clinicians and scientists who themselves are addicted to caffeine have a conflict of interest. They dare not (cannot) recommend that patients decrease or discontinue their use of caffeine because such advice might fall on deaf ears (or the physician might fear being hypocritical). Scientists dare not investigate caffeine because the negative results found might question their own judgment in using the substance.

Moreover, adding caffeine to products humans consume is a multi-billion, if not trillion, dollar business world-wide (e.g. caffeinated chewing gum, yogurt, ice cream, ad infinitim). No such businesses nor their shareholders want to see profit margins decrease. Additionally, those practicing medicine and the life/biomedical sciences think of young adults as healthy and in need of little medical advice/attention. How often have you sat in a doctor's waiting room next to 18-28 year olds? But those of us on university campuses know that student-caffeine queues are as ubiquitous as automobile queues at Dunkin's, Star Buck's and like drive-throughs. Caffeine's effects on the cardiovascular systems of young adults are worth investigating. Afterall, overweight and obesity, both risks for cardiovascular disease, among young adults runs as high as it does among the general U.S. adult population.

2. Methods

Participants---All subjects in this investigation were enrolled in Advanced Physiology at Rutgers University, Fall, 2021. They ranged from 20-25 years and averaged 22 years of age. Some were enrolled in graduate programs and a few others were post-baccalaureate students waiting to hear from graduate/medical schools. There were equal numbers of young men and young women, and they came from a variety of cultural and ethnic backgrounds. Because the experiment was an important part of course pedagogy and course final grades, no one was exempted from participating and there was no need for IRB review and approval.

All participants met with the author on two or three occasions outside of formal classroom hours. The first meeting was to discuss the experiment and to answer any questions/concerns participants had. The second meeting was to perform the experiment, and the third get-together was to review experimental results.

Instrumentation---Students arrived at the Merrill Laboratory either at 9 a.m. or 1 p.m. having avoided caffeine and caffeinated beverages for at least 24-48 hours. They assumed a supine resting position on a hospital examination bed and removed all jewelry and any stocking from their right foot. Electrocardiographic electrodes (ECG) were attached to the right wrist, left wrist and left ankle (standard Limb Lead I configuration, LLI). A large blood pressure cuff was wrapped around the right calf. It was

attached to a mercury manometer and had a built-in pressure gauge (LabTron, ADInstruments, Colorado Springs, CO). The blood pressure pulse in a centrally located pedal artery on the dorsal surface of the right foot was visualized/palpated, and a cardiomicrophone (model MLT201, ADInstruments, Colorado Springs) was placed over it and secured in place with Tegaderm adhesive film (3M Health Care, Neuss, Germany). A pulse plethysmograph (model TN1012/ST, ADInstruments, Colorado Springs) was attached to the ventral surface of the large toe and snuggly secured with a Velcro strap. The physiological transducers were attached to a PowerLab 8/35 data acquisition system and to a BioAmp preamplifier (channel 4, ECG recordings) (ADInstruments, Colorado Springs). The data acquisition system was attached to a desktop computer (Hewlett Packer) running Lab Chart analytical software (v. 8.1.19, 2021, ADInstruments). Room temperature was maintained at 22 ºC - 24ºC.

Experimental protocol---Subjects were asked to lie still for 20-30 minutes while monitored variables achieved their physiological steady states. Baseline data were then collected using monitored variables that included: ECG (LLI, mV), heart rate (HR, cycles per minute, cpm), systolic blood pressure (Ps, mmHg), diastolic blood pressure (Pd, mmHg), systemic mean arterial blood pressure (Pā, mmHg), digit volume (µl), digit blood flow (volume x HR, µl/min), calculated digital resistance to flow, i.e. peripheral vascular resistance (mmHg/µl/min), and reactive hyperemia (volume and flow) following a period of zero-flow ischemia and subsequent reperfusion. Reactive hyperemia consisted of occluding blood flow in the instrumented large toe for four (4) minutes (inflating the cuff to 200 mmHg) followed by release of the occlusion (deflation of the cuff), restoration of blood flow, and monitoring the flow response for sixteen (16) minutes.

After baseline data were collected (pre-caffeine) subjects consumed a 200 mg tablet of caffeine. A timer was set for sixty (60) minutes and monitored variables were recorded continuously or calculated at 15-minute intervals (e.g. peripheral vascular resistance). Students were asked to lie still, and, if possible, were even encouraged to catch a little sleep. The room lighting was dimmed, and noise/distractions were kept to a minimum. After 60 minutes a second set of data was collected. These data were labelled post-caffeine and were later compared, statistically, with pre-caffeine data.

Statistical analysis---All data were recorded on the desktop computer, were later extracted and reduced, then subjected to *a priori* statistical analysis. Initial variability between any two sets of pre- vs post-caffeine data was identified using ANOVA (repeated measures coupled with Tukey's w-procedure, LSD tests). Means were compared using Student's t-test for paired measures. All data are reported as means plus or minus (+/-) one standard error of the mean (s.e.m). Statistically significant differences were identified at $P<0.05$.

3. Results

An entire experiment, compressed horizontally, is illustrated in FIG. 1. One can see by comparison that pulsatile sounds, digital volumes, and blood flow in the toe were markedly reduced 60 minutes after consumption of 200 mg caffeine in this subject (2nd and 3rd panels from top). The reductions in volumes of the toes and blood flow to them were a consistent theme throughout all subjects.

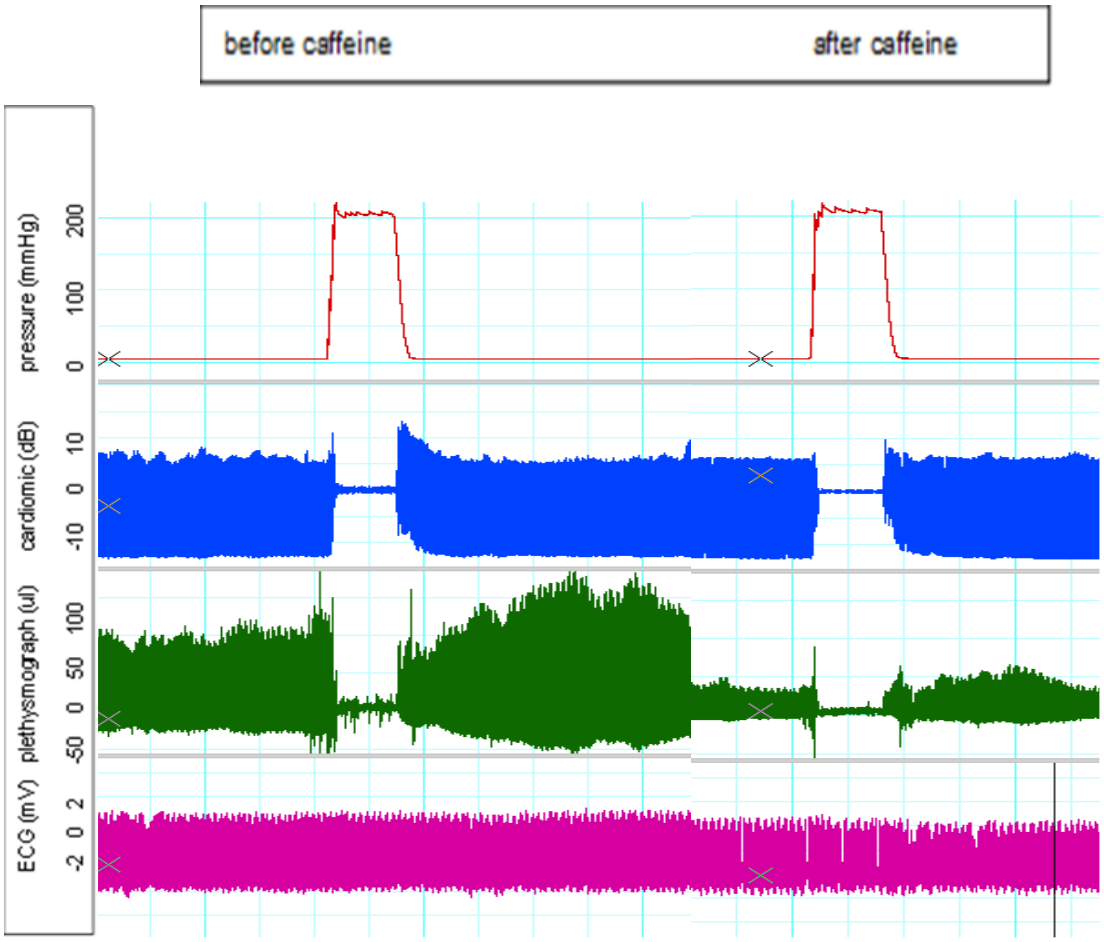

FIG. 1. **Illustration of a complete experiment. In panels two and three (from top) note the differences in sounds and volumes before and 60 minutes after subjects consumed a 200 mg dose of caffeine.**

Under the conditions of this experiment, caffeine had no significantly measurable effect on heart rate (FIG. 2, TABLE 1). Other than causing an unstable isoelectric line, caffeine also failed to influence ECG variables (e.g., wave amplitudes, segment lengths, intervals).

Systolic, diastolic, and systemic mean arterial blood pressures were all significantly elevated by caffeine at 60 minutes post-consumption (FIG. 3, TABLE 1). The changes amounted to about 25 mmHg increments in each case. Calculated peripheral vascular resistance was significantly and markedly elevated by caffeine at the same time (FIG. 4, TABLE 1). Although we did not systematically analyze responses at 15-, 30-, and 45-minutes the effects of caffeine on blood flow and blood pressure were visually evident as early as 15-30 minutes post-caffeine in most subjects (FIG. 1).

Both volume and blood flow in the toe were significantly ($P<0.05$) and markedly reduced by caffeine (FIG. 5). Again, these results were present at 60 minutes post-caffeine but were also evident as early as 15-30 minutes in most subjects. The reductions in volume and blood flow were consistent with the elevations in calculated peripheral vascular resistance.

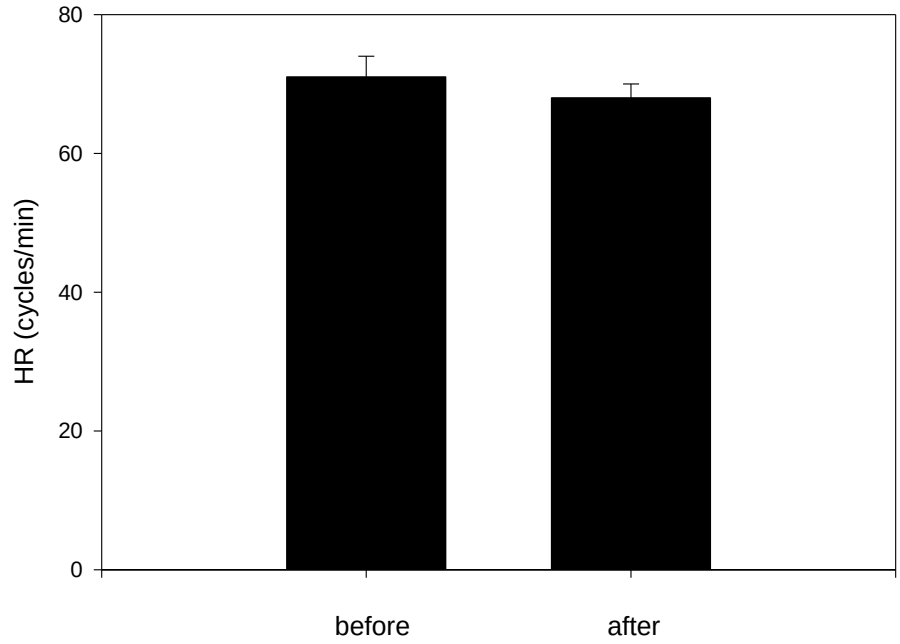

FIG. 2. **Under conditions of the current experiment, this figure illustrates a complete absence of effect of 200 mg caffeine on heart rate in our experimental subjects.**

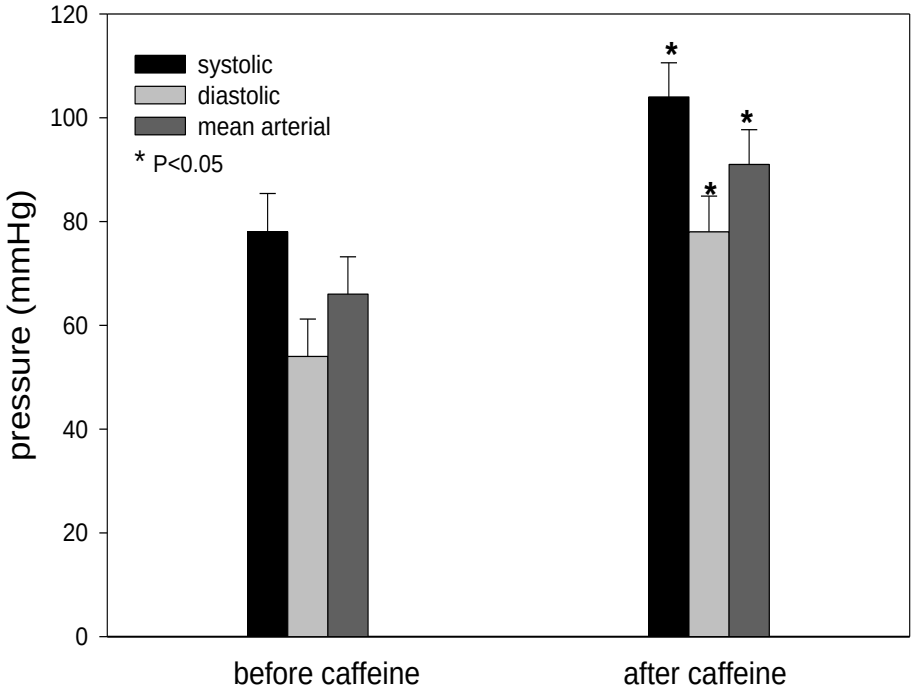

FIG. 3. **Caffeine consistently and significantly (P<0.05) increased systolic, diastolic, and systemic mean arterial blood pressures 60 minutes after its administration. Simultaneously, the drug consistently and significantly elevated calculated peripheral vascular resistance (see FIG. 5, also TABLE 1).**

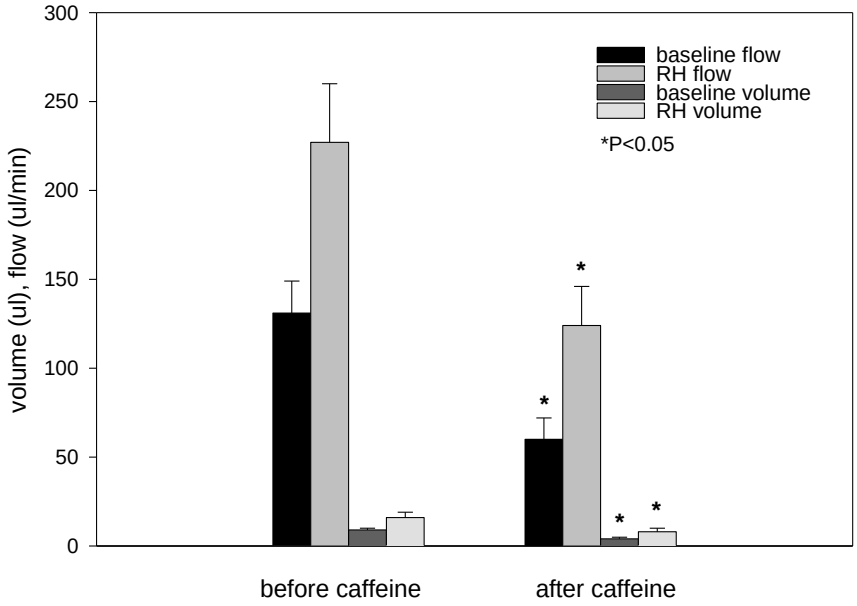

FIG. 4. **Caffeine significantly (P<0.05) and markedly reduced digital volume and digital blood flow. This occurred both under conditions of baseline measurements and during the peaks of reactive hyperemia following release of an occlusion lasting four minutes.**

Reactive hyperemia after four minutes of blood flow occlusion was significantly (P<0.05) and markedly attenuated by caffeine at 60 minutes (FIG. 1, FIG. 5). We made no effort to study hyperemia at 15, 30 or 45 minutes, but the 60-minute results are consistent with our previously reported data in young adults [1,2]. Four minutes of zero-flow ischemia and sixteen minutes of reperfusion are, arguably, models of clinical ischemia/reperfusion pathology.

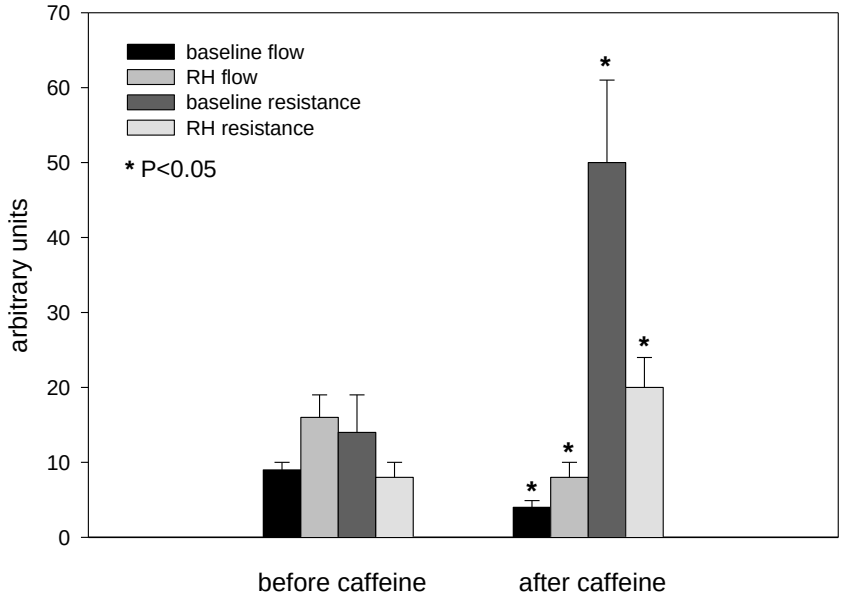

FIG. 5. **Caffeine significantly (P<0.05) and consistently increased calculated peripheral vascular resistance both under baseline conditions and during reactive hyperemia.**

TABLE 1. **Cardiovascular variables in young adults before and sixty minutes after taking 200 mg of caffeine orally.**

	before caffeine					after caffeine				
HR	Pā	vol	Q̇	PRU		HR	Pā	vol	Q̇	PRU
mean	71	66	227	16	8	68	91	124	8	20
sem	3	6	33	3	2	2	7*	22*	2*	4*

HR, heart rate (cycles per min, cpm); Pā, mean arterial blood pressure (mmHg); vol, volume (µl); Q̇, blood flow (µl/min); PRU, peripheral resistance units (mmHg/µl/min); *, $P<0.05$ relative to corresponding value before caffeine. All data are presented as means plus or minus one standard error of the mean (sem).

4. Discussion

Our experiment was designed to test the null hypothesis (H_O): caffeine impairs function of the peripheral circulation in young adults. The alternative hypothesis (H_A) was: caffeine does not impair function of the peripheral circulation in young adults. Because of the results we accepted our null hypothesis and rejected the alternative hypothesis.

The absence of well-designed, physiological, and pharmacological experiments on the topic of caffeine and the human cardiovascular system has encouraged the author(s) to try contributing to the field [1-4]. We chose ischemia and reperfusion as insults to the human cardiovascular system because they have experimental, medical, and pedagogical relevance.

Despite the sustained popularity of caffeinated drinks, especially coffee, there is a volume of circulating misinformation about its effects on the human cardiovascular system. For example, recent reports claim that consumption of coffee has surpassed consumption of water as the number one drink of choice among Americans [5]. How can this be? Coffee is a solution! The solvent is water, and the solutes are coffee beans. Can the volumetric consumption of coffee beans/ground granules surpass that of the very solvent in which they are dissolved (water)? The claim [5] is an impossibility and its sources are ignorance. As long as water remains the main solvent for dissolving coffee beans/granules, consumption of coffee cannot exceed consumption of water.

4.1 Extremes in the consumption of caffeine

As reported by the Nutrient Data Laboratory, USDA (Human Nutrition Research Center, Baltimore, MD), one 8-ounce cup of coffee (about 224 milliliters) contains approximately 100 milligrams of caffeine. Of more than fifty sports drinks and dietary supplements analyzed by the USDA, twenty-seven products, or more than one half, contained about 100-200 mg of caffeine (equivalent to 1-2 cups of coffee), eleven had 200-400 mg caffeine (2-4 cups of coffee), another eleven had 400-600 mg caffeine (4-6 cups of coffee) and at least four products provided 700-800 mg caffeine (7-8 cups of coffee). For patients already diagnosed with cardiovascular disease, Zheng and co-workers reported that higher consumption of coffee, tea and caffeine could increase the risk of all-causes of death, and cardiovascular death specifically [6].

Irritability, increased muscle tone, jitters, restlessness, and trembling have been reported in breastfed infants whose mothers claimed to drink multiple cups of coffee and other caffeine-containing beverages each day. In such cases, consumption of caffeine by these mothers could exceed 1000 mg per day. Infants' symptoms decrease a few days to two weeks after mothers stop consuming caffeine-containing beverages [7-11].

One physician reported drinking at least five mugs of coffee, four mugs of tea, and one can of cola daily while breast feeding two infants. One infant slept only briefly and woke easily. The second was fretful, hyperexcitable, and had poor sleep patterns until his mother stopped consuming caffeine. Another physician who reportedly drank 1.7-2.0 liters (~5.0-8.0 cups) of decaffeinated coffee daily had premature twins who both seemed to be irritable. When her coffee consumption increased further, the smaller infant suffered convulsion-like episodes. All symptoms resolved twenty-four hours after the nursing mother stopped consuming coffee [7-11].

Prenatal exposure to caffeine, including the widely recommended 'safe' dose (i.e., no more than 1.0 cup of coffee per day), has been associated with greater behavioral, developmental, and psychological complications. Greater body mass index (BMI) and consumption of soda were observed in children exposed to high doses of caffeine. Importantly, the association of externalizing problems with exposure to prenatal caffeine is comparable to that reported for prenatal exposures to both alcohol (12) and cannabis [13]. In laboratory animals, exposure to caffeine during pregnancy results in down-regulation of adenosine A_1 receptors, loss of neurons, and cognitive deficits in offspring [14-16].

4.2 Caffeine and transient ischemia/reperfusion in young adults

In the young adults in our experiment, 200 mg of caffeine failed to alter baseline, resting heart rate. The absence of effects of 100-400 mg of caffeine on heart rate has been a consistent outcome in our laboratory during the past several years [1-4]. A PubMed search of caffeine and heart rate, using no filters, yielded the following results: caffeine increases heart rate in adult humans (n=442 articles), caffeine decreases heart rate in adult humans (n=176 results), and caffeine has no effect on heart rate in adult humans (n=632 results) (applied October, 2022, covering the dates, mid-1960s-2022). Slightly more than one half of these investigations are consistent with our current findings, i.e., caffeine does not affect heart rate in adult humans. However, the disparate PubMed results also indicate broad confusion and disagreement on the topic.

Doing a similar PubMed literature search (October, 2022) using the phrases: caffeine increases peripheral blood flow in adult humans, caffeine decreases peripheral blood flow in adult humans, and caffeine has no effect on peripheral blood flow in adult humans reveals similarly-confusing results: n=23, n=17, n=29, respectively. Clearly, there have not been as many investigations on the latter topic as there have been on the topic of caffeine and heart rate. Still, there is general disagreement on the answer to the question. Much if not most of the disagreement could be caused, hypothetically, by the lack of investigator qualifications to study the question, and by the variability in methodologies applied.

Our experimental data reveal that caffeine attenuates the regulation of peripheral circulation in otherwise healthy young adults. In this case, four minutes of tissue ischemia would have caused a significant oxygen debt that needed to be repaid during reperfusion. However, the presence of caffeine, a vascular adenosine-receptor antagonist (and therefore a threat to the

physiological role of endogenous adenosine in regulating blood flow [17-23]), prevented reperfusion-induced reactive hyperemia and the needed delivery of compensatory oxygen. Failure to repay the oxygen debt was not the only limitation caused by caffeine. During the period of ischemia, the tissues would have also accumulated carbon dioxide and other byproducts of metabolism (e.g., oxygen radicals such as superoxide anion, hydroxyl radical, peroxynitrite, etc.) that should have been washed out during reperfusion. Thus, caffeine is harmful to the physiological homeostasis of oxygen supply and oxygen demand (oxygen balance). Few things can be more important to the maintenance of health and life than the physiological regulation of oxygen delivery and its use [24-26].

4.3 Caffeine and the regulation of peripheral blood flow

For many years scientists and others have had an interest in the regulation of blood flow to the digits [27-32]. These studies have been stimulated by an interest in the role of digital blood flow in thermoregulation [33-40]. The effects of caffeine on the peripheral regulation of blood flow is a relatively new phenomenon. In our laboratory in recent years, we have found that caffeine attenuates peripheral reactive hyperemia [2], pressure-flow autoregulation [3], and ischemia/reperfusion regulation (current study).

In the current study 200 mg caffeine taken orally as a tablet began affecting the cardiovascular system of young adults within fifteen minutes. Its inhibitory effects on digital volume and digital blood flow were fully expressed by sixty minutes. We don't know how long these effects might have lasted as sixty minutes represented the end of our experimental timeline. Blood flow during reperfusion and peak reactive hyperemia were reduced by about fifty per cent. These reductions in circulation were accompanied by 2-3 fold increments in calculated peripheral vascular resistance. Under our experimental conditions and in these young adults, caffeine is a marked and prominent peripheral vasoconstrictor and inhibitor of blood flow. Such caffeine-mediated interference with the regulation of blood flow is pathophysiological.

Some of our subjects provided unsolicited conversation about their uses of caffeine (i.e., other than as a stimulant for general study, examinations, etc.). Many use the toxicant as a pre-workout aid. Some describe 'tingling in the toes and fingertips' before and during their workouts. They also mentioned having cold fingers and toes and the general inability to get sound sleep in the presence of caffeine (personal communications). These and related subjective responses were not the purpose of our experiment, but they are consistent with our objective and statistically evaluated results. Caffeine's marked and significant attenuation of peripheral blood flow and its physiological regulation can explain most of the subjective responses.

5. Conclusion

The objective of our experiment was to determine if caffeine influences ischemia and reperfusion in the digits of young adults. We found that 200 mg of caffeine significantly decreased blood volume and blood flow in the toes of young adults during ischemia/reperfusion. Caffeine simultaneously and significantly increased the resistance to blood flow in these same digits. These detrimental caffeine-mediated responses are similar in males and females and across multiple cultures and ethnicities. Thus, we have accepted our null hypothesis and rejected the alternative hypothesis (see above). Caffeine, a methylxanthine, is a dangerous compound and most college students are unaware of it.

REFERENCES

1. Merrill GF, Joshi H. Caffeine and peripheral blood flow. J Clin Med Rev Rep. 2020:2(2):009.
2. Merrill GF, Costea DM, Sharp VA. Caffeine and reactive hyperemia. World J Cardiovas Dis. 2019;9(7):437-48.
3. Merrill GF, Costea DM, Sharp VA. Caffeine and pressure flow autoregulation. World J Cardiovas Dis. 2019;9(4):253-66.
4. Merrill GF, Sharp VA. Undesirable cardiovascular effects of hot drinks. Int J Clin Med Cases. 2018;1(3):117-24.
5. Coffee consumption hits two-decade high. Spring 2022 National Coffee Data Trends report. https://www.yahoo.com/now, New York, March 15, 2022.
6. Zheng H, Fan L, Xin L, et al. Association of coffee, tea, and caffeine consumption with all-cause risk and specific mortality for cardiovascular disease patients. Front Nutr. 2022;9:1-9.
7. Rivera-Calimlim L. Drugs in breast milk. Drug Ther. 1977;7(12):59-63.
8. Clement MI. Caffeine and babies. Br Med J. 1989;298:1461-7.
9. Rustin J. Caffeine and babies. Br Med J. 1989;299(6691):121-3.
10. Funk GD. Losing sleep over the caffeination of prematurity. J Physiol. 2009;587(Pt 22):5299-300.
11. Caffeine. National Library of Medicine (US): Drugs and Lactation Database, Bethesda, MD, URL:https://www.ncbi.nlm.nih.gov/books/Revised: April 19, 2021.
12. Lees B, Mewton L, Jacobus J, et al. Association of prenatal alcohol exposure with psychological, behavioral, and neuro- developmental outcomes in children from the Adolescent Brain Cognitive Development Study. Am J Psychiatry. 2020;177(11):1060-72.
13. Paul SE, Hatoum AS, Fine JD, et al. Associations between prenatal cannabis exposure and childhood outcomes: results from the ABCD Study. JAMA Psychiatry. 2020;78(1):64-77.
14. Lorenzo AM, Leon D, Castillo CA, et al. Maternal caffeine intake during gestation and lactation down-regulates adenosine A1 receptors in rat brain from mothers and neonates. J Neurosci Res. 2010;88(6):1252-61.
15. Silva CG, Metin C, Fazeli W, et al. Adenosine receptor antagonists including caffeine alter fetal brain development in mice. Sci Trans Med. 2013;5(197):197ra104.
16. Li Y, Zhang W, Shi R, et al. Prenatal caffeine damaged learning and memory in rat offspring mediated by ARs/PKA/CREB/BDNF pathway. Physiol Res. 2018;67(6):975-83.
17. Berne RM, Winn HR, Rubio R. The local regulation of cerebral blood flow. Prog Cardiovasc Dis. 1981;24(3):243-60.
18. Olsson RA. Local factors regulating cardiac and skeletal muscle blood flow. Ann Rev Physiol. 1981;43:385-95.
19. Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res. 1980;47(6):807-13.
20. Mustafa SJ. Cellular and molecular mechanism(s) of coronary flow regulation by adenosine. Mol Cell Biochem. 1980;31(2):67-87.
21. Feigl EO. Coronary Physiology. Physiol Rev. 1983;63(1):1-205.
22. Haddy FJ. Bioassay and pharmacologic evaluation of the adenosine hypothesis. Adv Exp Med Biol. 1977;78:175-82.
23. Burnstock G. The purinergic nerve hypothesis. Ciba Found Symp. 1977;48:295-314.
24. West JB. High Altitude and Man. West and Sukhamay Lahiri, Clinical Physiology Series. Rockville, Md: American Physiological Society, USA; 1984.
25. West JB. Everest The Testing Place. New York: McGraw-Hill Book Company, USA; 1985.

26. West JB. High Life: A History of High-Altitude Physiology and Medicine. Oxford: Oxford University Press, United Kingdom;1998.
27. Ye Y, Mauro M, Bovenzi M, et al. Reduction in finger blood flow induced by hand-transmitted vibration: effect of hand elevation. Int Arch Occup Environ Health. 2015;88(7):981-92.
28. Trager S, Pignataro M, Anderson J, et al. Color flow doppler: imaging the upper extremity. J Hand Surg. 1993;18(4):621-5.
29. Goodfield M, Hume A, Rowell N. Reactive hyperemic responses in systemic sclerosis patients and healthy controls. J Invest Dermat. 1989;93(3):368-71.
30. McDonnell AC, Eiken O, Mekjavic PJ, et al. Circadian rhythm of peripheral perfusion during 10-day hypoxic confinement and bed rest. Eur J Appl Physiol. 2014;114(10):2093-104.
31. Yan Y, Shen G, Xie K, et al. Wavelet analysis of acute effects of static magnetic field on resting skin blood flow at the nail wall in young men. Microvas Res. 2011;82(3):277-83.
32. Macefield VG. Cardiovascular and respiratory modulation of tactile afferents in the human finger pad. Exp Physiol. 2003;88(5):617-25.
33. Tischendorf F, Barbolini G, Curri SB. Histology, histochemistry, and function of the human digital arteriovenous anastomoses (Hoyer-Grosser's organs, Masson's glomera). II. The possible relationship with sweat glands. Microvasc Res. 1971;3(2):323-36.
34. Millard RW, Reite OB. Peripheral vascular response to norepinephrine at temperatures from 2 to 40 degrees C. J Appl Physiol. 1975;38(1):26-30.
35. Frech TM, Murtaugh MA. Non-invasive digital thermal monitoring and flow-mediated dilation in systemic sclerosis. Clin Exp Rheumatol. 2019;37(Suppl 119):97-101.
36. LeBlanc J, Dulac S, Cote J, et al. Autonomic nervous system and adaptation to cold in man. J Appl Physiol. 1975;39(2):181-6.
37. Victor RG, Leimbach WN, Seals DR, et al. Effects of the cold pressor test on muscle sympathetic nerve activity in humans. Hypertension. 1987;9(5):429-46.
38. Dishman RK, Nakamura Y, Jackson EM, et al. Blood pressure and muscle sympathetic nerve activity during cold pressor stress: fitness and gender. Psychophysiology. 2003;40(3):370-80.
39. Mourot L, Bouhaddi M, Regnard J. Effects of the cold pressor test on cardiac autonomic control in normal subjects. Physiol Res. 2009;58(1):83-91.
40. Merrill GF. Cardiovascular responses to a cold pressor test in college-age young adults. Int J Exper Clin Res. 2017;2017(1):1-6.