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Research Article

Caffeine and Pressure Flow Autoregulation

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Abstract

The benefits or detriments of caffeine on the human cardiovascular system have not been thoroughly studied and are still poorly understood. In a world where caffeinated beverages are evidently the adult drug of choice (e.g. coffee, energy drinks, soda, tea) investigating its effects on our bodies is of great importance. In this study we examined the effects of caffeine, taken as a tablet, on pressure-flow autoregulation. Young adults between 18 and 21 years of age were the experimental subjects. They were instrumented to monitor systemic arterial blood pressure, peripheral blood flow, calculated peripheral vascular resistance, and the electrocardiogram during an autoregulatory maneuver in the absence and presence of caffeine. Caffeine-mediated vasoconstriction was observed as early as 15 minutes after its consumption. Sixty minutes post-caffeine, vasoconstriction was so prominent that autoregulation was abolished. This was reflected, in part, as a significant reduction in blood flow that accompanied a 3-fold increase in calculated peripheral resistance and a significant increase in systemic arterial pressure. Heart rate was unaffected by caffeine under our experimental conditions. We conclude that caffeine has the ability to inhibit significant cardiovascular properties including pressure-flow autoregulation. Even though more work is needed, the significant caffeine-mediated changes in flow, pressure and resistance during autoregulation could have serious consequences for the cardiovascular system specifically, and for one's overall health in general.

INTRODUCTION

Caffeine is widely used for non-medical and medical purposes. It has various benefits such as respiratory stimulation in premature infants with sleep apnea [1,2]. However, it is most frequently consumed in beverages or as over-the-counter capsules, pills and tablets to boost one's energy [3-8]. Thus, abuse of caffeine has become a habit for many people even though there are unanswered questions about its effects on the body, especially the brain and cardiovascular system. Since caffeine is an adenosine receptor antagonist, adenosine-mediated circulatory regulation in the brain, heart, and elsewhere can be impaired by caffeine [9-12].

Although caffeine stimulates the central nervous system and can increase alertness there might be negative consequences that outweigh these effects. For example, we have recently reported that caffeinated hot coffee has dual, a physiological cardiovascular effects [13]. As a single bolus (swallow) of hot coffee passes through the esophagus it disturbs stability of the ECG, causing a wandering isoelectric line. Also, while hot coffee is stored in the stomach, thus significantly elevating gastric/body temperature, pronounced thermoregulatory peripheral vasodilation occurs (an attempt to eliminate excess stored heat). Peripheral vasodilation is followed by significant vasoconstriction, increased peripheral vascular resistance, and a marked reduction in blood flow [13].

In the current experiment we focused on the influence of caffeine on pressure-flow autoregulation. Results are consistent with our previous report [13], and demonstrate the need for much more work.

METHODS

Subjects

Experimental subjects were college-age young adults enrolled in courses at Rutgers University. Because this exercise was an integral part of the pedagogy of these courses it was exempt from IRB review and approval. Moreover, the activity was discussed in detail in class (e.g. experimental design, all subjects required to participate) and no identifying records were maintained or stored, therefore subjects were also exempt from providing informed consent.

Subjects were male and female from several cultural/ethnic backgrounds. They were either regular (daily) or irregular (weekly or less frequent) users of caffeinated beverages. All arrived at the laboratory having avoided caffeinated beverages for at least 24-48 hours.

Experimental design

Instrumentation---After subjects arrived at the laboratory they rested comfortably on a hospital examination bed in the

supine position. Room temperature was maintained at 22-24°C, and four physiological transducers were attached to each subject. These included a sphygmomanometer blood pressure cuff (Adult size, Index) with a built in pressure sensor (strain gauge balance). The cuff and pressure sensor were connected to a wall-mounted Baumanometer (model CE1562). A cardiomicrophone (model MLT201, ADInstruments, Colorado Springs, CO) was placed over the left brachial artery (near the antecubital fossa) and secured in place with Transpore, hypoallergenic surgical tape (3M Health Care, St. Paul, MN) and TegadermFilm (3M Health Care, Neuss, Germany). A pulse plethysmograph (model TN1012/ST, ADInstruments) was attached to the left index or middle finger (whichever presented the greater surface area) and snuggly secured with a Velcro strap. Heart rate was determined from a standard limb lead electrocardiogram (LLI, ECG).

Data acquisition system---All four transducers were attached to a PowerLab data acquisition system (model 8/35, ADInstruments) coupled to a desktop computer (HP Compaq LA2006x) running LabChart software (v. 8.1.12., September, 2018). All waveforms could be periodically or continuously displayed on a computer monitor for investigator observation.

Experimental protocol---Following instrumentation a timer was set, lights were dimmed, and a 15-minute period was allowed for monitored variables to achieve physiological steady state conditions. After 15 minutes steady state, baseline data were collected including: recordings of heart rate (HR, cycles per minute, cpm), ECG, systemic mean arterial blood pressure (Pa, mmHg), and volume in the index finger (µl per pulse). Multiplying pulsatile changes of volume of the index finger by heart rate yielded an estimate of finger blood flow (µl/min). Vascular resistance to blood flow in the instrumented finger could then be estimated by dividing mean arterial blood pressure by blood flow (mmHg/µl/min).

Subsequently, and on cue, the subject raised their fully-extended arms above the chest (heart) for five minutes. During this maneuver estimates of blood flow, blood pressure and resistance to blood flow were made (or calculated) at 45-60 seconds (before autoregulation) and again at 4-5 minutes (during autoregulation). On cue the subjects then lowered their arms to the pre-elevated resting position. Data collected during this pre-caffeine period were designated 'baseline'.

After baseline data were collected each subject consumed 400mg of caffeine (two tablets of 200mg caffeine each, NODOZ Alertness Aid, GSK Consumer Healthcare, Warren, NJ). The timer was reset for 60 minutes, and the subjects were asked to rest quietly with as little movement as possible. Hemodynamic variables were monitored by the data acquisition/computer system continuously. However, at 15-minute intervals we estimated blood pressure by inflating/deflating the pressure cuff (20-30 sec). Restoring finger blood flow (post-occlusion of the compressed brachial artery) and monitoring pulsatile arterial sounds (cardiomicrophone) could be used to estimate pulsatile and mean arterial blood pressures at these 15-minute timed intervals.

At 60 minutes post-caffeine the autoregulation maneuver described above was again completed. Data collected during this period were considered 'experimental' and were later compared, statistically, with the pre-caffeine data.

Statistics---The experiment was designed *a priori* and is a follow up to a related experiment conducted in our laboratory in the past year [13]. Initial variability was identified using Analysis of Variance for Repeated Measures (one-way ANOVA). Means were compared using Students t-test. All data are presented as means plus or minus one standard error of the mean (s.e.m.). Statistically significant differences were established at $P<0.05$.

RESULTS

Examples of entire experiments can be reviewed in Figures 1 and 2. The horizontal timelines have been compressed markedly to fit the 75+ minute experiment on single pages.

Heart rate---After fifteen minutes steady state baseline heart rate was 76 ± 2 cycles per minute. Heart rate did not change significantly during autoregulation before or after caffeine (e.g. 74 ± 2 vs 71 ± 2 cycles per minute 60 minutes after caffeine) (Figure 3).

Systemic mean arterial blood pressure was 79 ± 4mmHg under baseline conditions. Five minutes after raising arms pressure fell significantly to 52 ± 3 and 61 ± 4mmHg in the absence and presence of caffeine, respectively (Figure 4). Both means were significantly reduced compared to baseline, and 61 ± 4mmHg 60 minutes after caffeine was significantly greater than 52 ± 3mmHg before caffeine ($P<0.05$).

Blood flow to the instrumented finger was 88 ± 15µl/min under baseline, steady state conditions (Figure 5). This did not change significantly in the absence of caffeine after 4-5 minutes of raising one's arm above the heart. Conversely, in the presence of caffeine, blood flow during arm raising fell markedly and significantly to 29 ± 4.3 µl/min after 4-5 minutes, i.e. there was no evidence of flow autoregulation.

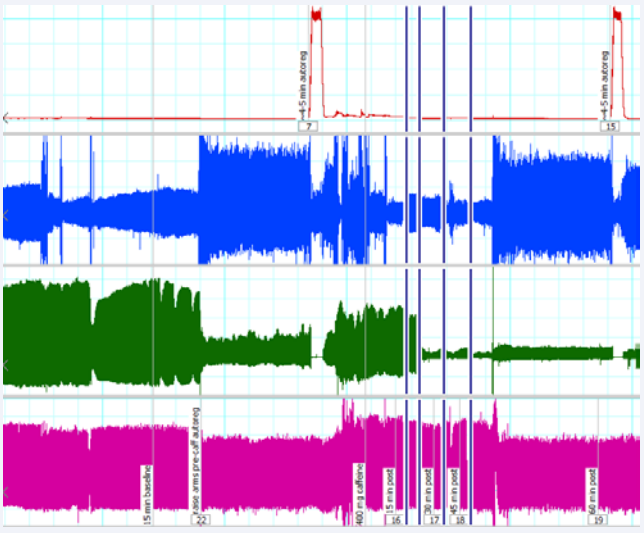

Figure 1 Representative tracing of a compressed complete experiment with the pressure channel (channel 1). Note the marked and significant reduction in finger blood flow in the presence of caffeine (autoregulation after). Compare details, especially in plethysmography (channel 3) before and after caffeine.

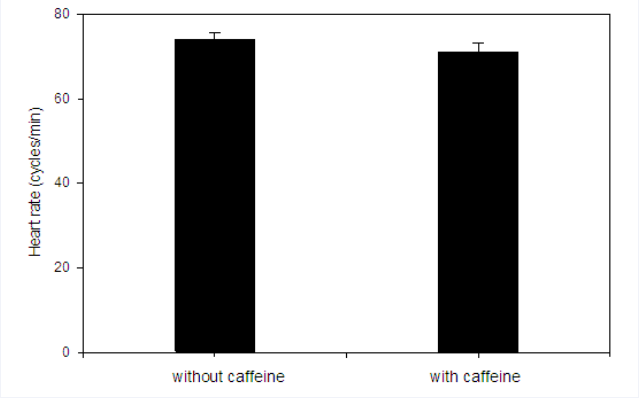

Figure 2 Heart rate. Note the absence of statistically significant differences in the absence and presence of caffeine. This is noteworthy because the literature reports caffeine-mediated increments and decrements in heart rate.

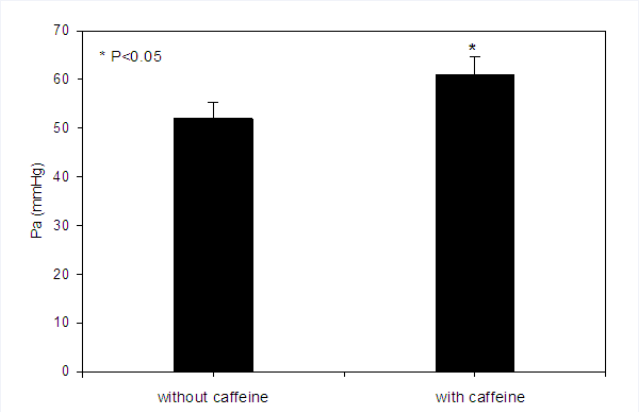

Figure 3 Systemic mean arterial blood pressure in the absence and presence of caffeine. Note the statistically significant elevation of blood pressure in the presence of caffeine.

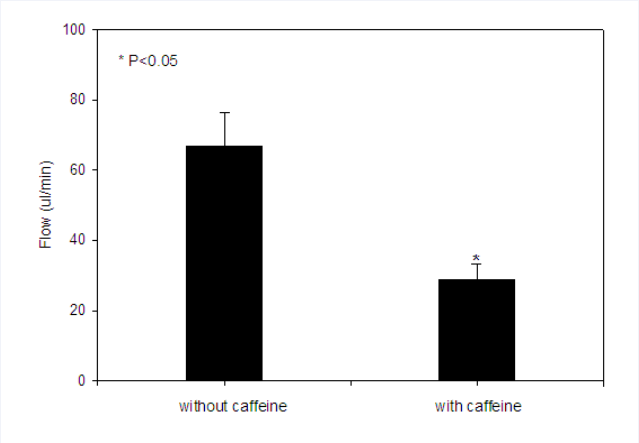

Figure 4 Blood flow in the absence and presence of caffeine. Note the statistically significant decrease in blood flow in the presence of caffeine. The hypoperfusion is consistent with caffeine-mediated elevation of peripheral vascular resistance (see Fig 6).

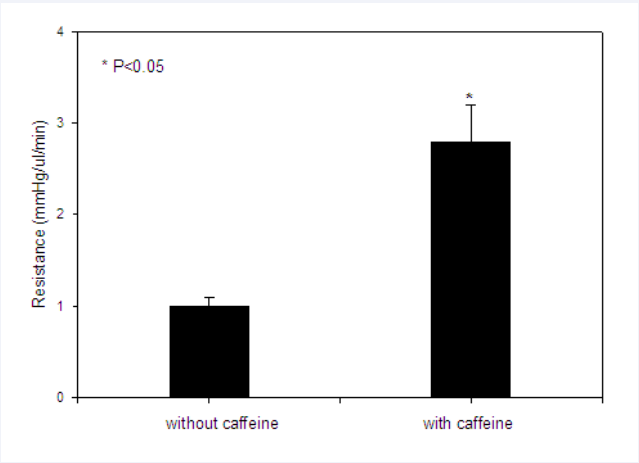

Figure 5 Resistance to blood flow in the absence and presence of caffeine. Note the marked and statistically significant elevation in resistance in the presence of caffeine. The increase in resistance, coupled with a reduction in flow, explains the increase in systemic mean arterial blood pressure caused by caffeine.

Peripheral vascular resistance under baseline conditions was 1.3 ± 0.2mmHg/µl/min (Figure 6). This remained unchanged at 1.0 ± 0.1 in the absence of caffeine but rose significantly to 2.8 ± 0.4mmHg/µl/min 60 minutes after caffeine ($P<0.05$). All hemodynamics are summarized graphically in Figure 6.

While the standard limb lead ECG was used primarily to measure heart rate, we did not notice acute effects of caffeine on waveforms, intervals and segments. For example, we did not see caffeine-induced ST-segment changes. Nor were ventricular premature beats (VPB), ventricular salvos (VS) or ventricular bigeminy (VB) evident with or without caffeine.

Subjective, non-quantifiable responses---Fifteen to thirty minutes post-caffeine several subjects reported feeling anxious and alert. From 30-60 minutes post-caffeine other subjects expressed having cold and/or tingling fingers and toes. Yet others had sweaty palms. Of these, a few mentioned sensations of numbness and 'needles and pins'. Others felt muscle tremors in the chest wall and upper extremities. One or two subjects experienced tightening of the chest and more vigorous heart beats, as well as mild headache 30-60 minutes post-caffeine.

DISCUSSION

Cerebral and cardiac effects of caffeine

A 20-year-old woman presented at a local hospital with severe agitation, tremor, and vomiting less than two hours after suicidal ingestion of concentrated caffeine (powder and tablets). Within minutes of arrival she experienced ventricular fibrillation. Defibrillation, intubation, and amiodarone administration temporarily resuscitated her but she subsequently experienced twenty three more episodes of pulseless ventricular fibrillation/tachycardia, each responsive to defibrillation. With additional treatment, including several weeks in a psychiatric unit, this patient made a full recovery. Her circulating plasma caffeine concentrations six and eighteen hours after ingestion were 240 and 150µg/ml [14].

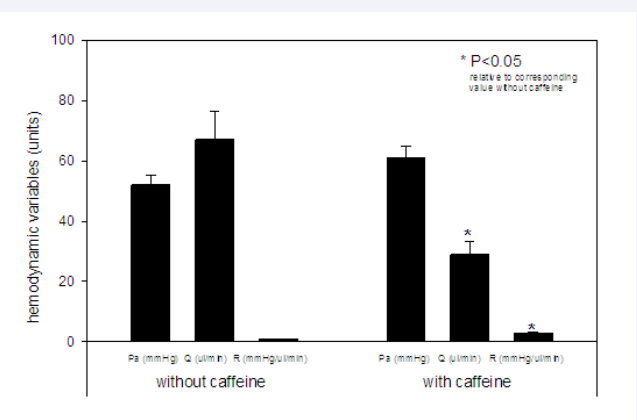

Figure 6 This is a composite illustration of Figs 4-6. Comparing all three hemodynamic variables that contribute to pressure-flow autoregulation, in the absence and presence of caffeine, presents a more complete picture of the experimental outcome.

A young man age sixteen collapsed at a high school in April, 2017, in South Carolina after consuming a McDonald's latte, a large Mountain Dew, and an energy drink in less than two hours. This 16-year-old died from a "caffeine-induced cardiac event causing a probable arrhythmia" the coroner said. He had no pre-existing heart condition (Reuters News Agency, April, 2017). These two reports provide recent and convincing evidence that caffeine can be lethal.

Cerebral vasoconstrictor effects of caffeine have been established for more than eighty years [15-20]. Between 1935 and 2017 investigators reported a reduction in cerebral blood flow caused by intravenous and/or oral administration of caffeine. Mathew saw these effects as early as thirty minutes after oral administration of 250 or 500mg caffeine [19]. Responses to the two doses were not significantly different. More recently Merola, using functional MRI (fMRI), observed significant effects of caffeine on the cerebral extraction of oxygen (16% increase), cerebral blood flow (30% decrease) and cerebral oxygen consumption 19% (decrease) [21].

We did not measure indices of oxygen consumption in our investigation. Peripheral blood flow did decrease markedly. It is not unreasonable, therefore, to speculate that oxygen metabolism would have also been affected. Thus, caffeine has powerful cardiovascular and cerebrovascular effects in otherwise healthy young adults.

Caffeine and autoregulation of blood flow

Our motivation to investigate caffeine began a few years ago when I tried to design an experiment using students enrolled in a seminar course. I planned to divide the class in two, those who did and who did not consume caffeinated beverages [13]. Finding young adults on or off university campuses who do not consume caffeinated beverages is a virtual impossibility.

By standards of classic experimental physiology autoregulation of blood flow is defined as the ability of an organ/tissue to maintain a relatively constant blood supply over a wide range of systemic arterial blood pressures [22-26]. The typical approach to investigating this phenomenon in an experimental animal laboratory is to instrument an organ (e.g. kidney, heart, skeletal muscle) so its blood supply can be measured during and shortly after adjustments in arterial blood pressure [22]. In the current experiment we instrumented conscious young adults so peripheral blood flow to a digit, and the arterial driving pressure needed to perfuse the digit, could be estimated. After a 15-minute baseline period, which included measurements of blood flow and blood pressure, we asked the supine subjects to fully extend their arms and hands above the heart for five minutes.

By changes in gravitational and hydrostatic forces, this procedure initially reduced blood pressure and blood flow to the instrumented finger (first 30-60 seconds). In the absence of caffeine, and by a combination of metabolic, myogenic, and neurogenic mechanisms, blood flow to the finger was partially restored over the next 4-5 minutes even though blood pressure was still significantly reduced (e.g. 52 ± 3 vs 79 ± 4mmHg, $P<0.05$). Sixty minutes after consuming 400mg of caffeine, and in the same subjects, blood flow was less than half its pre-caffeine value when the same arm-raising procedure was repeated. That is, no evidence of pressure-flow autoregulation was seen in the presence of caffeine.

At the same time blood pressure was modestly but significantly elevated when compared to corresponding values in the absence of caffeine. Calculated peripheral vascular resistance in the instrumented finger had increased by almost 3-fold above the pre-caffeine level. This was not surprising. Within 15 minutes of consuming caffeine, blood flow to the instrumented finger began to decrease. The steady decline in blood flow continued until reaching its nadir about 45-60 minutes after caffeine. That is, caffeine produced rapid and sustained peripheral vasoconstriction.

Caffeine and adenosine

Adenosine is a ubiquitous physiological regulator of organ and tissue blood flow [25,27-31]. Adenosine's vasodilator properties were first reported by Robert Berne et al., in the early 1960s [31]. Later, Ray Olsson et al., were among the first to begin work on identifying cardiac/vascular adenosine receptors [32-35]. Since those initial discoveries many review articles about adenosine's physiological properties and signal transduction pathways have been published [36,37].

Caffeine (1,3,7-trimethylxanthine) is one of several

Table 1: Cardiovascular variables before (baseline, pre-caffeine) and sixty minutes after consuming caffeine.

Autoregulation		
Baseline	**Pre-caffeine**	**Post-caffeine**
HR (cpm)		
76 ± 2	74 ± 2	71± 2
Pa (mmHg)		
79 ± 4	52 ± 3	61 ± 4*
Flow (µl/min)		
88 ± 15	67 ± 9	29 ± 4*
R (mmHg/µl/min)		
1.3 ± 0.2	1.0 ± 0.1	2.8 ± 0.4*

methylxanthines that recognize and bind to adenosine receptors in a pharmacologically competitive manner [38-40]. Caffeine is commonly-consumed by Americans and others, including pregnant women where harm can befall the fetus in utero and post-parturition [41]. For example, administration of caffeine to pregnant rats not only affects the dam but also affects the fetuses [42]. Maternal and fetal plasma concentrations of caffeine are indicative of equal exposure to the drug. Fetal ECGs can exhibit more extensive caffeine-mediated changes than are seen in the dams' ECGs. The frequency of ectopic beats and abnormal T waves are directly related to plasma concentrations of caffeine in the fetus [42].

Moreover, in humans maternal consumption of caffeine during early days/weeks of pregnancy reduces birth weight and size of offspring. Under such conditions caffeine also has lasting detrimental effects on heart and cardiovascular function [37]. For example, caffeine impairs ubiquitous signaling properties of adenosine in the fetal heart (e.g. disruption of DNA methylation), and these pathophysiological, epigenetic effects can last well beyond the exposed generation [37]. The developing fetal heart lacks the enzymes needed to metabolize and detoxify methylated products [37].

SUMMARY AND CONCLUSIONS

Since the distal segments of human fingers contain skeletal muscle one would expect them to display some degree of autoregulation. In the current study mean arterial pressure in fingers of the initially-elevated arms dropped significantly below baseline values. So did flow, however, during the next four to five minutes and in the absence of caffeine, flow returned to levels that were not significantly different from baseline values, i.e. the finger autoregulated blood flow. Conversely, after 60 minutes of caffeine the finger did not autoregulate its blood supply.

By some reports, 50-60mmHg is the lower end of the autoregulation range [22]. Therefore, one might not have expected flow to be fully restored at these arterial pressures. However, in our experience in healthy young adults, blood pressure is well below the standard 120/80mmHg. Therefore, one might also expect the autoregulatory range to be modified in healthy young adults. That remains to be investigated. Still, caffeine's marked vasoconstrictor properties and accompanying significant increment in calculated peripheral vascular resistance prevented autoregulation in the current experiment.

LIMITATIONS

Despite the above conclusions, there are limitations to this investigation. For instance, we examined only one elevation in pressure. In an experimental animal laboratory, at least two or three elevations and two or three reductions in pressure would have been investigated. Secondly, we did not measure finger blood flow directly (e.g. ultrasonically, electromagnetically). We calculated blood flow by multiplying plethysmographic changes in finger volume during single cardiac cycles by heart rate, thereby indirectly estimating blood flow. Thirdly, we did not take into consideration the potential variability in caffeine tolerance among subjects. Ideally we would have divided subjects into those who do and do not consume caffeinated beverages. Finding nonconsumers on university campuses, as already mentioned, is difficult.

Regardless of these and other limitations the results are clear and unambiguous. In the presence of caffeine blood flow to the finger was unable to autoregulate. This was due to early and sustained caffeine-mediated vasoconstriction in the peripheral vasculature. That these vasoconstrictor properties are not limited to the periphery is evident from clinical reports of caffeine-mediated cerebral and coronary vasoconstriction. Additional physiological investigations of caffeine and the human cardiovascular system are needed.

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