The Physiological Effect of Temperature, Physical Exercise, and Caffeine on the Heart's Rhythmic Cycle of Contraction in the Human Cardiovascular System.

Author(s): Christe Marbbn, Anuj Sharma

November 19, 2009

Key Words: Cardiovascular System, Heat Stress, Cold Stress, Physical Exercise, Caffeine

ABSTRACT **The aim of this study was to assess the effects of hot and cold temperature exposure, physical exercise, and caffeine ingestion on various cardiovascular system response parameters in humans. For this purpose, the heart's rhythmic cycle of contraction and volume pulse were monitored and measured electrically via an electrocardiogram. To measure the effects of temperature, subjects were exposed to moderately warm water (50ºC) and ice water (0ºC) on the surface of their forearm using a plastic bag. The effects of hand and leg exercise on the cardiovascular system were measured by squeezing a hand dynamometer and by walking stairs, respectively. The effects of caffeine were measured after subjects had consumed 250 ml of unsweetened coffee, an equivalence of 100 mg's of caffeine. It was found that heat stress, physical exercise, and caffeine ingestion induced a stimulatory effect on cardiovascular response, while cold stress generated an opposite response. It is suggested that the cardiovascular response pattern reported during physical exercise and heat stress is partially due to increased core temperature, which functions as a major factor driving active sympathetic vasodilator activity. In this manner, the opposite is true during cold stress, which stimulates vasoconstriction. Finally, it is possible that caffeine blocks the biochemical process leading to vasoconstriction. These findings indicate that once a stressor is exerted on the subject, cardiovascular response is altered in a manner where blood flow is ultimately modified.**

INTRODUCTION

The human cardiovascular system is a complex and extensive network that involves the heart, blood vessels, the circulating blood, and its cellular components. These components function in concert as interdependent systems to move nutrients, gases, and wastes to and from cells to keep all body systems functioning at optimum efficiency. Humans possess a closed cardiovascular system, as opposed to one that is opened; this means that the blood is confined to vessels and is distinct from the interstitial fluid. Closed systems offer the advantage of transporting circulatory fluids effectively at higher blood pressures, allowing humans and other vertebrates to meet high metabolic demands of cells, tissues, and organs (Badeer & Hicks, 1992).

The rhythmic beating of the heart is a ceaseless activity that pushes blood around the body. A chamber of the heart contracts when an electrical impulse moves across the sinoatrial node. This signal depolarizes the node and the depolarization spreads rapidly via the internodal pathway, through the Bundles of His and Purkinje fibers, causing the atria and ventricle to contract (Lange & Brooks, 1977). Heart action is generally thought to be regulated solely by autonomic nerves and humorally transmitted agents such as catecholamines (Brooks & Lange, 1977). Therefore, cardiac muscle is myogenic; its rhythmical contractions arise within the muscle tissue.

Resting heart rate is influenced by many variables, namely, cardiorespiratory fitness, the use of stimulants or depressants, and environmental factors, such climate and altitude. Caffeine is a well-known stimulant shown to cause increases in blood pressure and systemic vascular resistance under resting conditions (Daniels *et al.,* 1998). It is an adenosine-receptor antagonist, and adenosine can cause vasodilation in several regional circulations (Daniels *et al.,* 1998). As a result, blockade of adenosine receptors could cause cardiovascular and hormonal effects similar to those induced by caffeine. In order to understand the effects of caffeine and various other factors on the heart's rhythmic cycle of contraction, the heart's electrical impulses must be closely monitored. An electrocardiogram (ECG) displays the voltage between pairs of electrodes on different sides of the hearts, indicating the overall electrical activity of the heart during the cardiac cycle.

In light of these observations, the underlying purpose of this experiment is to investigate whether various stressors, such as temperature changes to the skin, physical exercise, and caffeine will have any direct effect on human cardiac physiology. Changes to volume pulse, heart rate, and peripheral circulation patterns in ECG recordings will be used to dictate whether any changes occurred to the heart's rhythmic cycle of contraction. Since muscle contractions cause the release of adenosine, blockade of adenosine receptors might account for caffeine's reported cardiovascular effects (Ballard *et al.,* 1988); thus, it is predicted that the caffeine contained in coffee will induce a stimulatory effect on the cardiovascular system. Moreover, since vascular muscle tone is regulated via various vasoactive substances synthesized by vascular endothelial cells and released during physical exercise (Berry *et al.,*

1997), it is predicted both hand and leg exercises will promote increased blood flow, which will, in turn, increase heart rate and pulse volumes by stimulating receptors lining the blood vessels. Finally, since warmer temperatures, as opposed to colder temperatures, tend to dilate cutaneous vascular beds and divert blood from skeletal muscles to skin (Kamijo *et al.,* 2008), it is predicted that heat stress will augment the variables used to measure cardiac response, either through the release of local paracrine agents, such as nitric oxide or by the secretion of catecholamines, such as epinephrine, in response to warm-sensitive neurons (Ajisaka *et al.,* 2003). In contrast, colder temperatures will induce the opposite effect in order to prevent the loss of bodily heat.

MATERIALS & METHODS

The Effect of Temperature Variations on Volume Pulse. Male and female subjects were connected to three electrodes: a positive lead on the right wrist, a negative lead on left wrist, and a grounded lead on the right leg. The electrodes were subsequently attached to an ECG device (model IWX/214, iWorx). In addition, a pulse plethysmograph (model PT-104) was attached on the volar surface of the subject's distal segment of the middle finger. After a minute of quiet resting, a bag containing ice cold water (0ºC) was placed on the subject's left forearm. ECG and volume pulse recordings following the removal of the bag were used to indicate the recovery progress leading to homeostasis. Similarly, the effect of heat stress was measured by placing a bag of warm water (50ºC) on the subject's left forearm. The information obtained from the ECG was used to calculate pulse wave amplitude (volts), beat period (seconds/beat), heart rate (BPM), and R-Pulse (seconds).

ECG and Volume Pulse after Leg Exercise. The same group of subjects were instructed to perform a random physical exercise that utilized leg muscles, such as linear jumping or walking stairs, for three minutes. Immediately following the exercise, ECGs formatted to show pulse and pulse integral were recorded until the subject's heart rate and breathing rates returned to normal – baseline. The information obtained from the ECG was used to calculate the average R-wave amplitude (volts), beat period, heart rate, P-R interval (seconds), Q-T interval (seconds), T-P interval (seconds), R-pulse interval, and pulse wave amplitude at 30 second intervals throughout the recovery period.

ECG and Volume Pulse after Hand Exercise. Subjects connected to the ECG device were instructed to sit quietly while grasping a hand dynamometer (model FT-325) with the plethysmograph attached to their middle finger. Subjects rhythmically squeezed the dynamometer bulb until the forearm muscles fatigued. Immediately following the exercise, ECGs were recorded until the amplitude of the finger signal attained a reasonably constant level. The information obtained from the ECG was used to calculate the subject's heart rate at rest and at 30 second intervals into the recovery period, the average R-pulse amplitude, R-wave amplitude, and pulse wave amplitude.

ECG and Volume Pulse after Coffee Consumption. Male subjects selected for this study were instructed to drink one cup of unsweetened coffee containing approximately 100 milligrams of caffeine. Subjects had fasted two hours prior to treatment and were non-smokers. Following consumption, subjects were immediately connected to an ECG with a plethysmograph attached to their middle finger. The information obtained from the ECG was used to calculate the average beat period, heart rate, R-pulse interval, and pulse wave amplitude.

Statistical Analysis. Significant differences observed between ECG measurements taken at rest versus measurements taken at each variable tested were determined by the Student *t*-test using Sigmaplot. Data are presented as means ± standard error; statistical significance was accepted at $P \leq 0.05$.

RESULTS

The Effect of Temperature Variations on Volume Pulse. The effects of cold and heat stress on peripheral circulation and heart rate is summarized in Figure 1 and Figure 2, respectively. When cold stress was applied to the forearm, mean pulse wave amplitude decreased by nearly 42 percent, while mean heart rate decreased by seven percent compared to values obtained at rest (Figure 1). Within two minutes of recovery, both cold-induced increases returned to baseline levels. Variations in changes in R-pulse interval throughout the exposure and recovery periods were negligible since only slight changes (<5 percent) were verified. This treatment provided no *significant* changes to cardiovascular responses.

When heat stress was applied to the forearm, mean pulse wave amplitude significantly increased (P=0.001) by 249 percent, while heart rate significantly increased (0.017) by 19 percent, compared to values obtained at rest (Figure 2). Within two minutes of recovery, both heat-induced increases returned to baseline levels. Moreover, heat stress also significantly decreased R-pulse frequency

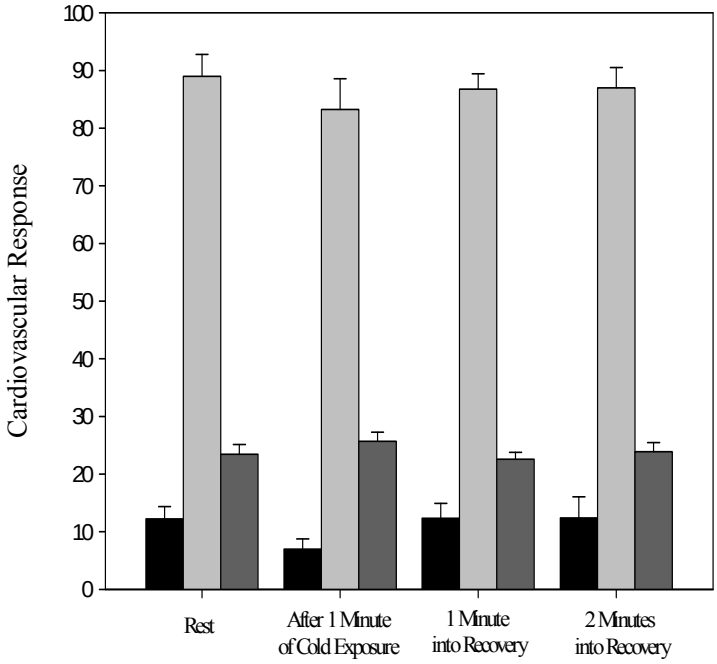

Figure 1. The effect of cold stress on heart rate (□) (BPM), plethysmographic pulse wave amplitude (■) (volts×10^2), and R-pulse interval (▒) (seconds×10^2) in human cardiovascular response. No significant differences at 95% were noted in all three intervals analyzed using Student's *t*-test. Values are the means of *n*=7 determinations ± standard error. Note: Significance testing was only performed on values obtained at *rest* versus *1 minute into recovery*.

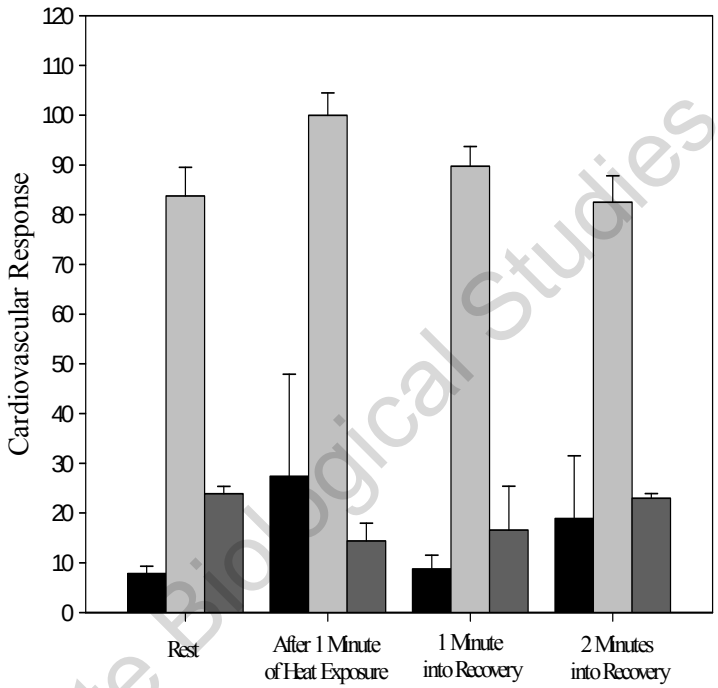

Figure 2. The effect of heat stress on heart rate (□) (BPM), plethysmographic pulse wave amplitude (■) (volts×10^2), and R-pulse interval (▒) (seconds×10^2) in human cardiovascular response. Significant differences at 95% were noted in all three intervals documented using Student's *t*-test. Values are the means of *n*=7 determinations ± standard error. Note: Significance testing was only performed on values obtained at *rest* versus *1 minute into recovery*.

(P=0.033) from 0.2388 ± 0.0147 seconds to 0.1444 ± 0.0357 seconds, following one minute of exposure. Similar to pulse wave amplitude and heart rate, R-pulse frequency gradually returned to baseline levels after two minutes of recovery.

ECG and Volume Pulse after Leg Exercise. Changes in parameters of cardiovascular response evoked by performing a leg exercise are expressed in Table 1. Immediately after performing linear jumps or walking stairs for three minutes, significant changes were observed in beat period, heart rate, R-wave amplitude, P-R interval, Q-T complex, T-P interval, and R-pulse interval, compared to data obtained at rest (baseline). At zero recovery, heart rate significantly increased (P≤0.001) by 64 percent. Although heart rate gradually started to decline, it remained 21 percent higher than values recorded at baseline after a 150 second rest period, thus exerting a profound effect on blood circulation. This trend was also observed in all eight parameters recorded, indicating that a recovery period longer than 150 seconds is required to return values back to baseline levels. Moreover, immediately after the

ECG and Volume Pulse after Hand Exercise. Changes in parameters of cardiovascular response evoked by squeezing a hand dynamometer are expressed in Table 2. Immediately after performing this exercise, significant changes were noted in beat period, heart rate, R-pulse interval, and R-wave amplitude, compared to data obtained at rest. At zero recovery, heart rate significantly increased (P=0.009) by 15 percent. Like the effects observed when jumping, heart rate gradually decreased beyond time zero recovery, but remained nearly ten percent higher than values recorded at baseline, thus exerting a profound effect on blood circulation. This trend was also evident in the three other parameters which showed significance, indicating that a recovery period longer than 150 seconds is required to return values back to baseline levels. Moreover, immediately after the exercise session, the remaining parameters showed significant *decreases* (range, 9–39 percent).

Table 1. The effect of leg exercise on various cardiovascular response parameters after jumping up vertically or walking stairs for three minutes.

Cardiovascular Response Parameters	Mean Recovery Period ± Standard Error					Difference at 95% Confidence[1,2]
	Rest	0	30	60	150	
R-wave Amplitude (volts)	0.7656 ± 0.0542	0.6097 ± 0.0392	0.6268 ± 0.1581	0.6780 ± 0.1796	0.6896 ± 0.1700	Significant, P=0.033
Beat Period (seconds)	0.6966 ± 0.0146	0.4224 ± 0.0046	0.4835 ± 0.0236	0.5330 ± 0.0373	0.5841 ± 0.0410	Significant, P≤0.001
Heart Rate (BPM)	86.25 ± 1.8428	142.25 ± 1.4361	125.5 ± 6.1847	114.0 ± 8.1138	104.5 ± 7.5000	Significant, P≤0.001
P-R Interval (seconds)	0.1648 ± 0.0088	0.1070 ± 0.0105	0.1376 ± 0.0217	0.0839 ± 0.0143	0.1373 ± 0.0135	Significant, P=0.006
Q-T Complex (seconds)	0.3364 ± 0.0107	0.2823 ± 0.0068	0.2674 ± 0.0149	0.2827 ± 0.0259	0.3025 ± 0.0251	Significant, P=0.005
T-P Interval (seconds)	0.1857 ± 0.0068	0.0804 ± 0.0120	0.1159 ± 0.0109	0.1428 ± 0.0218	0.1860 ± 0.0158	Significant, P =<0.001
R-Pulse Interval (seconds)	0.2123 ± 0.0035	0.1630 ± 0.0049	0.2418 ± 0.0708	0.1713 ± 0.0071	0.1856 ± 0.0135	Significant, P=<0.001
Pulse Wave Amplitude (volts)	0.1149 ± 0.0184	0.0806 ± 0.0307	0.1747 ± 0.0891	0.1844 ± 0.0849	0.1365 ± 0.0308	Not significant, P =0.376

[1] Significance is based on differences at rest versus 0 time recovery
[2] P-values obtained from Student *t*-test.
[*] n = 7

The most profound decrease, aside from beat period, was the mean R-pulse interval, declining from 0.3066 ± 0.0914 seconds to 0.1868 ± 0.0146 seconds. No significant changes were noted in the results of pulse wave amplitude.

ECG and Volume Pulse after Coffee Consumption. The effects of caffeine ingestion contained in coffee on peripheral circulation and heart rate is summarized in Table 3. Upon consuming the 250 ml cup of coffee, heart rate (88.0 ± 8.7321) increased by 34 percent to 118.0 ± 6.0817. On the contrary, beat period, pulse wave amplitude, and R-pulse interval decreased. Aside from beat period, the greatest magnitude of decrease was observed in pulse wave amplitude, declining from 0.1503 ± 0.0028 volts to 0.1045 ± 0.0104 seconds (30 percent). This data shows a similar pattern to what was observed when heat stress was applied to the forearm.

Table 2. The effect of hand exercise on various cardiovascular response parameters after rhythmically squeezing a dynamometer for three minutes.

Cardiovascular Response Parameters	Mean Recovery Period ± Standard Error					Difference at 95% Confidence[1,2]
	Rest	0	30	60	150	
Beat Period (seconds)	0.6770 ± 0.0228	0.5836 ± 0.0156	0.6141 ± 0.0233	0.6377 ± 0.0341	0.6217 ± 0.0302	Significant, P=0.065
Heart Rate (BPM)	89.0 ± 3.0277	102.5 ± 2.5495	98.25 ± 4.0697	95.25 ± 5.6771	97.5 ± 5.2678	Significant, P=0.009
R-Pulse Interval (seconds)	0.3066 ± 0.0914	0.1868 ± 0.0146	0.2231 ± 0.0136	0.2186 ± 0.0189	0.2244 ± 0.0131	Significant, P=0.001
R-wave Amplitude (volts)	0.6664 ± 0.1530	0.5898 ± 0.0217	0.5721 ± 0.0350	0.6001 ± 0.0535	0.5787 ± 0.0105	Significant, P=0.036
Pulse Wave Amplitude (volts)	0.1311 ± 0.0395	0.1184 ± 0.0337	0.1625 ± 0.0465	0.1485 ± 0.0621	0.2033 ± 0.0630	Not significant, P=0.816

[1] Significance is based on differences at rest versus 0 time recovery.
[2] P-values obtained from Student *t*-test.
[*] *n* = 7

DISCUSSION

The results of this investigation provide evidence that heat and cold stress, physical exercise of the legs and hands, and caffeine ingestion induce physiological effects on various cardiovascular system response parameters in humans. When cold stress was applied to the forearm, mean pulse wave amplitude and heart rate decreased compared to the control. When the subject's forearm is exposed to the ice-cold surface of the bag, sensory afferents at the area of exposure trigger a systemic sympathetic activation leading to marked vasoconstriction (Lafleche *et al.,* 1998). This elevates pulse pressure by narrowing the blood vessels, increasing the resistance, and in turn, decreasing the rate at which the heart beats, due to catecholamine release, such as norepinephrine. This is in accordance with the finding that full-hand immersion into water at 5ºC (the cold pressor test) yields an increase in blood norepinephrine concentration (Besnard *et al.,* 2000).

When norepinephrine is released by the autonomic nervous system into the bloodstream, it binds to α1-adrenoreceptors found on endothelial cells lining the blood vessels. This activates a G-protein coupled receptor which leads to smooth muscle contraction (Eschenhagen, 2008). In fact, several authors have observed that local cooling induces vasoconstriction in distant areas of the

Table 3. The effect of caffeine ingestion (100 mg) contained in coffee beverage on cardiovascular responses.

Cardiovascular Response Parameters	Mean ± Standard Error	
	Rest	Two Minutes after Consumption
Pulse Wave Amplitude (volts)	0.1503 ± 0.0028	0.1045 ± 0.0104
Beat Period (seconds)	0.6833 ± 0.0130	0.5117 ± 0.0492
Heart Rate (BPM)	88.0 ± 8.7321	118.0 ± 6.0817
R-Pulse Interval (seconds)	0.25 ± 0.0028	0.2063 ± 0.0083

* $n = 2$

body (Gooden *et al.,* 1976). Therefore, it is possible that the cold had exerted its effect around the body, rather than just locally. The data obtained in this experiment is consistent with the hypothesis that, acute decreases in heart rate and cardiac output are associated with the exposure to cold temperatures. One possible reason why mean pulse wave amplitude, heart rate, and R-pulse intervals did not shown *significant* differences before and after treatment, may be due to the methodology used for cooling the surface of the forearm. For instance, the forearm may have inadequately been covered by the ice-bag's surface area, restricting the subject's forearm from full exposure. A more effective means of approaching this experiment would be to fully submerge the subject's hand into an ice water bath to accurately measure the stressors effect on the heart.

When heat stress was applied to the forearm, mean pulse wave amplitude and heart rate significantly increased compared to the control. It has been shown that heat stress induces a thermoregulatory process known as vasodilation, as opposed to vaso*constriction*, to increase blood flow. Cutaneous vasodilation during heat stress promotes heat dissipation from body core to skin by increasing the diameter of blood vessels, and thus, decreasing resistance (Kamijo *et al.,* 2008). As resistance decreases, the subject's cardiac output – a parameter equal to the heart rate multiplied by the volume of blood ejected during ventricular systole – also increases, which, in turn, causes a rise in the mean arterial pressure (Kamijo *et al.,* 2008). It is possible that vasodilation may explain the significant increases observed in pulse wave and heart rate.

Cutaneous vasodilation during heat stress is induced through two mechanisms: (1) Withdrawal of sympathetic vasoconstrictor activity, and (2) enhancement of an active sympathetic vasodilator system (Kamijo *et al.,* 2008). It is assumed that the heat emitted from the bag of warm water may have stimulated the peripheral warm-sensitive neurons that mainly belong to unmyelinated C-fiber afferents found in the peripheral nerves of somatic sensory system (Kamijo *et al.,* 2008). The input of this sensory information to the hypothalamic temperature-regulating centers would contribute to the initiation of active cutaneous vasodilation, either through the release nitric oxide, bradykinin, or adenosine by local paracrine agents from endothelial cells or by the secretion of catecholamines such as epinephrine (Ajisaka *et al*. 2003). Although further biochemical investigations are required to accurately monitor this process, the data obtained in this experiment is consistent with the proposed hypothesis in the view that acute increases in heart rate and cardiac output are associated with exposure to elevated temperatures.

The present data shows a close relationship between the effects of mild leg exercises and increases to heart rate and volume pulse. Like the effect exerted during heat stress, physical exercise also stimulates the body's core temperature, which functions as a major factor driving active sympathetic vasodilator activity (Kamijo *et al.,* 2008). Berry *et al.,* (1997) demonstrated that a 30-minutes bout of moderate cycling using both legs decreased pulse wave amplitude; this phenomenon was also observed in the experiment conducted. Pulse wave amplitude is a common variable used to index the measurement of arterial wall stiffness (elasticity) (Ajisaka *et al.,* 2003). The lower the artery stiffness, the higher its buffering capacity; a high buffering capacity suggests that the artery can efficiently absorb the energy during pulsatile blood flow and reduce the energy loss by making the blood flow smooth (Ajisaka *et al.,* 2003). Consequently, during an exercise, it is favourable that arterial stiffness (pulse wave amplitude) decrease, in order to increase blood flow and meet the oxygen demands in active muscles (Ajisaka *et al.,* 2003).

In a similar experiment formed performed by Ajisaka *et al.,* (2003), it was suggested that the increase in heart rate and decrease in pulse wave amplitude (arterial stiffness) may be attributed to regional factors, such as increases in temperature, exercising muscle-derived metabolites (adenosine, potassium), and flow-mediated vasodilators (nitric oxide) – all of which might contribute to vasodilation of vascular smooth muscle. In particular, the production of nitric oxide, which is a potent endothelial vasodilator, has been shown to reduce the vasoconstrictor response to α-adrenoreceptor stimulation and increase blood flow associated with acute exercise (Collins *et al.,* 1993). Therefore, it is possible that the exercise-induced differences observed between the post-exercise changes to heart rate and pulse volume are due to the release of nitric oxide. However, the data obtained cannot fully specify

which factor is actually responsible; this is a limitation of the present experiment.

Since the general effect of physical exercise is increased blood flow throughout the body, it is possible that the cardiovascular effects observed during the hand exercise experiment occurred via a similar process mentioned above. The data obtained in both experiments is consistent with the hypothesis that, acute physical exercise of the hands and legs will stimulate cardiac response.

The results obtained after performing the caffeine investigation provide evidence that caffeine alters cardiovascular response in humans. A 100 milligrams dose of caffeine increased heart rate, while pulse wave amplitude and R-pulse interval decreased. A decrease in pulse wave amplitude suggests that aortic stiffness has decreased. However, in a study conducted by Hirata *et al.,* (2003), it was discovered that pulse pressure increased significantly after caffeine had been administrated, denoting an *increase* in aortic stiffness. This inconsistency may be due to one of two reasons: (1) The study conducted by Hirata *et al.*(2003) was based on a higher dose of caffeine (250 mg), or (2) an inadequate number of subjects (n=2) took part in the present experiment; thus, significance could not be attributed. Therefore, although caffeine increases heart rate, the mechanism it uses to stimulate a cardiovascular response must differ than that exerted by physical exercise, as predicted in our hypothesis. The caffeine induced alterations in this study were probably due to antagonism of adenosine receptors. When caffeine binds to α1 and α2 adenosine receptors (Boekema *et al.,* 1987), unbound adenosine attenuates the release of epinephrine from the adrenal medulla (Graham *et al.,* 1993). Since epinephrine is a potent vasoconstrictor, the more caffeine available, the greater the heart rate since blood vessels are not vasoconstricted (Daniels *et al.,* 1998).

Caffeine may have also exerted its effects on cyclic adenosine monophosphate (cAMP), a second messenger ubiquitously expressed and shown to be involved in many metabolic pathways, including those activated by epinephrine via β-adrenoreceptors (G-protein coupled receptor). When caffeine is present, the enzyme responsible for dephosphorylating cAMP – phosphodiesterase – is inhibited. This causes cAMP to persist in cells for a longer period of time, activating cAMP-dependent protein kinases, which subsequently phosphorylates enzymes that lead to cellular responses similar in nature to those observed in this study. Likewise, when cytosolic cAMP concentrations are high, calcium channels located on the plasma membrane open. An increase in cytoplasmic calcium causes smooth muscle contraction. Therefore, it is possible that the cAMP produced by adenylate cyclase, following the activation of β-adrenoreceptors, was active for a longer period of time due to caffeine's inhibitory effect on cellular phosphatases.

In summary, the findings presented in this study suggest that external changes in temperature, physical exercise, and caffeine can influence the cardiovascular system through multiple mechanisms. Since many of the models used to describe the physiological processes that took place are based on biochemical reactions, further molecular and biochemical investigations are required to resolve these details. In addition, these results also suggest that ECG recordings and volume pulse are excellent tools for investigating symptoms and signs associated with various cardiovascular system complications.

REFERENCES

Ajisaka, R., Kuno, S., Maeda, S., Matsuda, M., Otsuki, T., Sugawara, J., & Tanabe, T. (2003). The Effects of Low-Intensity Single-Leg Exercise on Regional Arterial Stiffness. *Japanese Journal of Physiology*, 53: 239-241.

Ballard, H. J., Cotterrell, P., & Karim, F. (1988). Role of adenosine in exercise vasodilation. In: *Vasodilation: Vascular Smooth Muscle, Peptides, Autonomic Nerves and Endothelium,* New York: Raven.

Badeer, H. S., & Hicks, J. W. (1992). Gravity and the circulation: "open" vs. "closed" systems. *Regulatory, Integrative and Comparative Physiology*, 262(5): 725-732.

Berry, K. L., Cameron, J. D., Dart, A. M., Jennings, G. L., & Kingwell, B. A. (1997). Arterial compliance increases after moderate intensity cycling. *American Journal of Physiology, Heart and Circulatory Physiology*, 273: 2186-2191

Besnard, Y., Bittel, J., Cottet-Emard, J., Launay, J. C., Pequignot, J., Savourey G., & Sendowski, I. (2000). Sympathetic stimulation induced by hand cooling alters cold-induced vasodilation in humans. *European Journal of Applied Physiology*, 81:303–309.

Boekema, P., De Abreu, R., Smits, P., & van't Laar, A. (1987). Evidence for an antagonism between caffeine and adenosine in the human cardiovascular system. *Journal of Cardiovascular Pharmacol*ogy, 10: 136–143.

Collins, H. L., DiCarlo, S.E., & Patil, R.D. (1993). Acute exercise enhances nitric oxide modulation of vascular response to phenylephrine. *American Journal of Physiology, Heart and Circulatory Physiology*, 265: 1184–1188.

Daniels, J. W., Mole, P. A., Shaffrath, J. D., & Stebbins, C. L. (1998). Effects of caffeine on blood pressure, heart rate, and forearm blood flow during dynamic leg exercise. *Journal of Applied Physiology*, 85: 154-159.

Eschenhagen, T. (2008). B-adrenergic signalling in heart failure – Adapt of Die. *Natural Medicine*, 14: 485-487.

Gooden, B. A., Hayward, J. M., & Holmes, W. F. (1976). Cardiovascular reflexes in man to a stream of cold air. *Circulation Research*, 10: 691–696.

Graham, T. E., Sathasivam, P., Spriet, L., & Van Soeren, M. H. (1993). Caffeine metabolism and epineprine responses during exercise in users and nonusers. *Journal of Applied Physiology*, 75: 805–812.

Hirata, K., O'Rourke, M. F., Stefanadis, C., Toutouza,s P., & Vlachopoulos, C. (2003). Caffeine increases aortic stiffness in hypertensive patients. *American Journal of Hypertension*, 16(1): 63-66.

Kamijo, Y. I., Lee, K., & Mack, G. W. (2008). Active cutaneous vasodilation in resting humans during mild heat stress. *Journal of Applied Physiology*, 98: 829–837.

Lafleche, A. B., Laloux, B., Pannier, B. M., & Safar, M. E. (1998). Arterial response during cold pressor test in borderline hypertension. *American Journal of Physiology, Heart and Circulatory Physiology*, 275: 409-415.

Lange, G., & Brooks, C. M. (1977). Interaction of myogenic and neurogenic mechanisms that control heart rate. *The Proceedings of the National Academy of Sciences*, 74(4): 1761-1762.