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The effects of caffeine ingestion on the hemostatic response to simulated firefighting activities

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Dedication

I would like to dedicate my thesis to my loving parents, Paul and Stacy. Their unequivocal support has been nothing less than a blessing throughout my time as both an undergraduate and graduate student. Without their values, paramount work ethic, and encouragement, I would never have found such success. From their humor at my most stressful times to their wisdom and guidance when I felt astray, I owe my highest achievements to these two wonderful people. Thank you for teaching me to believe in God, myself, and my dreams.

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Last, but certainly not least, I would like to dedicate this piece to my boyfriend, Jason. His unconditional love and understanding throughout this entire program reinforced my drive to succeed. He introduced me to the firefighting profession, and his unwavering dedication as a firefighter serving our community inspired me to conduct this research. My family is the most caring, entertaining and hardworking bunch of people I have come to know, and these qualities are what have helped build the path to my success. Thank you all for being the most loving and supportive family one could hope for.

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Abstract

Sudden cardiac events are the leading cause of death among firefighters, and it is acknowledged that most ischemic events are due to an occlusive thrombus formation. In addition, due to the demanding job requirements and shift work, firefighters commonly overuse caffeine. The purpose of this study was to examine the potential effects of caffeine on the hemostatic response to simulated firefighting activity. Twelve healthy male firefighters (age, 31.3 ± 5.4 yrs; weight, 94.2 ± 13.1 kg; BMI, 28.7 ± 2.9 $kg \cdot m^{-2}$) participated in this study, wearing full personal protective equipment (PPE) and self-contained breathing apparatus (SCBA). Subjects completed two trials of a simulated firefighting activities course after consuming either 6mg/kg BW of caffeine or placebo one hour prior to exercise. Blood samples and air levels from the SCBA were obtained pre-exercise and post-exercise, and time to completion was recorded. Factor VIII and tissue plasminogen activator (tPA) activity increased post-exercise and plasminogen activator inhibitor-1 (PAI-1) activity decreased post-exercise in both conditions. There was a significant treatment x exercise interaction for Factor VIII levels as they increased more in the caffeine trial. There was a trend ($p = 0.05$) for increased air consumption in the caffeine condition versus placebo condition. Results from the present study suggest that caffeine elicits a higher coagulation response without concomitant increases in fibrinolysis during simulated firefighting.

Chapter One

Introduction

Firefighting is considered to be one of the most hazardous and physically demanding occupations held by civilians (16). While performing their duties on the fireground, firefighters operate under both physiologically and psychologically stressful conditions. They are generally subjected to hot environments in addition to wearing heavy personal protective equipment (PPE), also known as turnout gear, which increases their level of physiological strain. The combination of variable environmental conditions, strenuous work, heavy and insulating PPE, and psychological stress can lead to significant cardiovascular and thermal strain for firefighters (24). Additionally, most firefighters work 24-hour shifts and go for extended periods of time without sleep, leading to increased caffeine intake (3), cardiovascular strain and risk for cardiovascular disease (2, 30).The high rate of deaths due to sudden cardiac events are of particular concern since they account for approximately 45% of all line-of-duty deaths in the fire service (8).

The metabolic demands of firefighting require firefighters to work at near maximal heart rates for extended periods of time (11, 24, 28), in the presence of thermal and psychological stressors. Sothmann et al. reported that during actual emergencies, individual heart rates and oxygen uptake (VO_2) increase to 84-100% and 63-97% of maximal heart rate and maximal oxygen consumption (VO_{2max}), respectively (28). The National Fire Protection Association (NFPA) recommends a minimum VO_{2max} of 42 $mL/kg \cdot min^{-1}$ for firefighters due to the high energy requirements (21). The heavy PPE required in firefighting activities consists of safety boots, heavy fire-resistant outer garments (pants, coat), a fire-resistant hood, gloves, a helmet, and a self-contained breathing apparatus (SCBA) which is used in conjunction with a full-face mask. This PPE contributes an additional mass to each firefighter of about 18 to 24 kg, of which the majority is attributed to the SCBA/mask (19). While the SCBA/mask are not worn in all fireground activities, incidents involving fire suppression require these pieces. The duties performed at fire suppression incidents increase relative risk of fatal cardiac events 10-100 fold, making the inclusion of the SCBA/mask in this study a necessity (16). The bulky PPE, while essential, has been proven to increase effort and time to complete tasks on the fireground, especially among those who are not physically active on a daily basis (15, 19, 31). The added weight and the decreased mechanical efficiency due to the required turnout gear increases the metabolic demand for each firefighter.

Most ischemic events and an even greater proportion of exertion-related ischemic events occur due to an occlusive thrombus (10). Therefore, it is possible that myocardial infarctions triggered by firefighting are at least partially due to alterations in hemostasis. In support of this, intense physical exertion has been shown to actuate changes in both coagulation and fibrinolysis, even in short bouts of exercise, increasing risk for sudden cardiac event in the post-exercise period through increases in coagulation potential (7, 12, 13, 18, 20, 26, 32). Hedge et al. examined the changes in hemostasis in the one hour period after submaximal running, finding that both coagulation and fibrinolysis were elevated post-exercise; however, elevated coagulation activity was sustained for at least an hour post-exercise while fibrinolytic activity had returned to baseline shortly after exercise cessation (13). Huskens et al. reported a shift towards greater pro-coagulant responses following strenuous exercise, with a more pronounced effect on males than females (14). This is of particular importance since the majority of firefighters are males.

Firefighting activities have been reported to increase acute coagulability (4, 25, 27). Specifically, Smith et al. and Burgess et al. observed that live firefighting activity significantly increases platelet number and coagulation potential, increasing the likelihood for an ischemic event shortly after the firefighting activities (4, 27). While fire suppression activities put firefighters at risk for cardiac emergencies, the lifestyle factors attributed to most firefighters may also increase the likelihood of experiencing a sudden cardiac event.

Firefighting, like many other emergency-related and life-protecting occupations, requires employees to work shift work or for several hours at a time without adequate sleep. Shift work is associated with several negative health effects, many of which contribute to increased cardiovascular disease risk. Bogglid et al. reported in a meta-analysis that shift work alone increased the cardiovascular disease risk by 40% (2). In a specific study among firefighters, those performing shift work presented with higher subjective fatigue and decreased physiological functioning (30). To battle the fatigue and disrupted sleep cycles as a result of shift work, ergogenic aids are often utilized; the most popular being caffeine (23). Shift work is associated with increased caffeine intake (3, 22), and has been reported to be overused among some firefighters (5). While there is some evidence for an ergogenic effect of caffeine during exercise (6), the effect of caffeine on thermoregulation and cardiovascular disease should also be considered. Kellawan et al. demonstrated that significant amounts of caffeine may increase core body temperature while performing activities in PPE, increasing thermal strain and risk for illness among firefighters (17). Caffeine may also enhance the production of muscle metabolites during exercise in the heat that cause reflex cardiovascular responses (29).

There still exists a large gap in knowledge on the specific effects of caffeine on coagulation potential at rest and during exercise. Gebhard et al. demonstrated *in vitro* the potential for caffeine to enhance prothrombotic activity of endothelial cells (9). In a recent unpublished study from our laboratory, we observed a significant increase in coagulation potential post-exercise when combined with caffeine consumption (1). The combination of heavy insulated PPE, strenuous physical exertion, and other physiologically stressful factors of shift work and firefighting present unique challenges, and the effects of caffeine on the cardiovascular system under these conditions are unknown. Therefore, in light of the consequences cardiac emergencies pose for individual firefighters and public safety, it is important to investigate the potential combined effects of caffeine and firefighting activities on coagulation and fibrinolysis. It is hypothesized that caffeine intake prior to simulated firefighting activities will increase coagulation potential to a greater degree than simulated firefighting activities without caffeine supplementation.

Assumptions:

For the purposes of this study, it will be assumed that environmental conditions will not have an effect on experimental outcomes. Both trials will be performed at a temperature within the range of 45-70°F and at a humidity no greater than 70%, ensuring consistency. It is also assumed that the simulated firefighting tasks performed during this study are a good representation of the tasks and workload that are performed on the fireground during a real emergency situation.

Limitations:

A potential limitation of this study is the inability to generalize conclusions to the entire population of firefighters, as several other factors not accounted for in this study play a role in increasing coagulation, such as gender, age, prior health history and any current medications. Another limitation is the inability to generalize results to firefighters actively participating in fire suppression. While the activities performed in this study strongly resemble those performed on the fireground during live-fire emergencies, it should be noted that stressors are likely to be more significant in a true emergency, having a greater effect on hemostasis than observed in this experiment. The results of this study are also limited to the specific activities involved in firefighting, and cannot be generalized to any form of strenuous work duty of similar intensity.

Delimitations:

In order to obtain consistent results and to draw accurate conclusions from the data, the subjects involved in this study were all adult male firefighters aged 18-45 years who are medically cleared by their employing fire department. This study also represents ingesting a standard dose of caffeine based on body mass, rather than the normal amount reported by subjects on a daily basis.

Definition of terms:

The term ‘coagulation potential’ is used frequently, as much of the literature concerning exercise and hemostasis refers to the potential for coagulation to occur due to increased coagulatory factors, while coagulation *per se*, may or may not be occurring. The ‘fireground’ refers to the entire scene/location where firefighting activities are occurring.

Chapter Two

Methodology

Participants

The participants will be twenty apparently healthy male firefighters. Because the menstrual cycle affects hemostasis, data collection will occur in males only. Participants will be career firefighters to ensure familiarity with exercise in personal protective ensemble (PPE) and the self-contained breathing apparatus (SCBA). All participants will be recruited from the Harrisonburg Fire Department and will be tested at the Harrisonburg Fire Department Training Grounds. To eliminate higher risk subjects, medical history will be obtained via survey using a Health Status Questionnaire, and only those with documented medical clearance by a physician in the past 12 months may be included in this study. Subjects will be free from anticoagulant medications and will be between 18 and 45 years old. Subjects may be allowed to participate even if at a low or moderate ACSM risk level, since this study will not expose them to any physical or psychological demands beyond their normal duties as firefighters. Participants will be recruited through informal presentations/discussions of the study at monthly fire department meetings. This study was approved by the Institutional Review Board of James Madison University.

Testing protocol

Prior to testing, there will be a preliminary session at which time participants will sign an informed consent document (See Appendix A) indicating that they understand the benefits and risks of participation in this study and that their participation is voluntary.

They will also complete a Health Status Questionnaire (See Appendix B) and Caffeine Habits Questionnaire (See Appendix C). Any firefighters indicating that they have a history of coagulation disorders and are taking any medications affecting coagulation will be excluded from the study. Subjects will be required to abstain from caffeine, alcohol and tobacco 24 hours prior to testing, as well as fast for 10 hours prior to testing.

Supplementation: Prior to each trial, the subject will drink 500mL of either a placebo (water with no-calorie lemon flavoring) or caffeine preparation, administered in random counterbalanced order and double-blind fashion. The caffeine beverage will contain 6 mg/kg body weight of anhydrous caffeine dissolved in 500 mL of water with identical lemon flavoring as the placebo. The participant will then wait for one hour before beginning the simulated activities, performing only light activities such as preparing apparatus and gear for his shift.

Simulated Firefighting Testing: A double-blind, random counterbalanced experimental design will be used with each participant performing two trials of the simulated firefighting activities. The trials will be identical except for the ingestion of either caffeine (CAFF) or placebo (PLA) prior to the simulation test. For each subject, the two trials will be separated by at least 14 days. Simulated firefighting activities will be performed while wearing full PPE that is NFPA 1971-compliant at the Harrisonburg City Fire Training Grounds (Morning Pride turnout gear, Cairns 10-10 helmet). Participants will also wear an MSA Firehawk SCBA with a 60-minute carbon-fiber air cylinder. The average weight of a full set of PPE with SCBA is 29 kg. Prior to resting blood sampling, subjects will assume a seated position for 15 minutes. While remaining in the seated position, a resting venous blood sample will be obtained. Participants may then don their mask and hood and enter the training course, accompanied by a fire department safety officer. Once the simulated activity as described is complete, the participants will immediately return to the designated recovery area, assume a seated position and provide post-simulated activity blood samples within two minutes of activity cessation. Air usage and time to completion of the simulated activities will be recorded.

The simulated firefighting activities will take place on fire training grounds that include a two-story training building surrounded by an open gravel area containing fire equipment, including two ladders, one 80 kg training dummy, one hose roll, one charged hose line, a ventilation sled, five traffic cones, various tools, and a simulated ceiling-pulling station equipped with weights (See Figure 1). Participants will enter the simulated firefighting course at ground level, climb up a 3.7 meter ladder to the second floor, gain entry through a window and crawl 18 meters where they will reach a set of stairs. At this point, they are to stand up and walk down the fourteen steps to the ground level where an 80 kg training dummy is located. Subjects are required to drag the dummy 9 meters around the interior of the building, drop it at a doorway, and walk 15 meters to exit the building. Once outside, the participant will pick up a roof ladder weighing 20 kg, carrying it 22 meters around the exterior of the building. At the rear of the building, the ladder will be placed on the ground and a rolled section of hose (17 kg) will be picked up and carried 22 meters to the front of the building. Once the hose is placed on the ground, participants will walk 10 meters to the next station where they will use a 4 kg rubber sledge hammer to drive a ventilation sled (72 kg) approximately 0.6 meters. Participants will walk 10 meters to pick up a charged hose line, which will then be advanced forward 6 meters, the nozzle will be opened momentarily, closed, and then the charged line will be retreated back to the starting point. After walking 25 meters to the next station, the participants must alternate moving softballs and baseballs sitting on top of five traffic cones over 10 meters in order to test dexterity. Lastly, participants will walk 12 meters to the simulated ceiling-pulling station where they will be required to use a pike pole to complete two sets of four pushing and four pulling motions, for a total of sixteen repetitions, working against a 36 kg weight. The participant will walk 10 meters back to the starting point and this sequence of training obstacles will then be repeated, with every subject completing two full laps of the simulated firefighting activities course. These testing procedures are designed to mimic the tasks that take place during actual fire suppression duties during an emergency call and should be sufficient to elicit a similar metabolic and cardiovascular response. The design is similar to that of the Candidate Physical Ability Test that is required to be passed by firefighters to prove they are capable of entering a training academy and is used during biannual evaluations.

Blood sampling, assays

For the pre and post samples, 10 mL of blood will be drawn from an antecubital vein. Half of this sample will be drawn into acidified citrate collection tubes (Tcoag, Inc.; Mount Olive, NJ), while the other half will be drawn into a normal citrate solution (Becton-Dickinson; Franklin Lakes, NJ). Samples will be centrifuged immediately for 20 minutes at 4,500xg and 4°C to obtain platelet-poor plasma, and then frozen and stored at -80°C until assayed. Plasma concentrations of factor VIII levels, tPA activity, and PAI-1 activity will be determined using commercially available ELISA kits (VisuLize® Ontario, Canada; Eagle Bioscience, Inc, Nashua, New Hampshire) according to manufacturer specifications. Plasma from samples collected in normal citrate tubes will be used for Factor VIII assays, while samples from the acidified citrate collection tubes will be used to assay for tPA and PAI-1 activities.

Statistical analysis

Subject characteristics will be depicted using descriptive statistics. Changes in each hemostatic variable will be analyzed using repeated-measure analysis of variance, with exercise (pre- and post-activity) and treatment (caffeine, placebo) as within-subjects factors. Post-hoc tests will be done using paired t-tests to assess testing condition (caffeine, placebo). Paired t-tests will also be used to compare time to completion of the course and air consumed during the course. Statistical significance for all analyses is set at alpha (α) = 0.05.

Chapter 3

Manuscript

Introduction

Firefighting is considered to be one of the most hazardous and physically demanding occupations (23). While performing their duties, firefighters operate under both physiologically and psychologically stressful conditions. Additionally, most firefighters work 24-hour shifts and for extended periods of time without sleep, leading to increased caffeine intake (4), cardiovascular strain and risk for cardiovascular disease (3, 42). The high rate of deaths due to sudden cardiac events are of particular concern since they account for approximately 45-50% of all line-of-duty deaths in the fire service (13). The metabolic demands of firefighting require work at near maximal heart rates (17, 36, 40), in the presence of thermal and psychological stressors. The heavy personal protective equipment (PPE) required in firefighting also contributes 18 to 24 kg of additional mass to each firefighter (27), increasing the metabolic demand of firefighting activities.

Most ischemic events, especially exertion-related ischemic events, occur due to an occlusive thrombus (16). Therefore, it is possible that myocardial infarctions triggered by firefighting are at least partially due to alterations in hemostasis. In support of this, intense physical exertion has been shown to actuate changes in both coagulation and fibrinolysis, even in short bouts of exercise, increasing risk for sudden cardiac events in the post-exercise period through increases in coagulation potential (12, 19, 20, 26, 30, 38, 43). Hedge et al. observed that both coagulation and fibrinolysis were elevated after submaximal running; however, elevated coagulation was sustained for at least an hour post-exercise while fibrinolytic activity had returned to baseline shortly after exercise cessation, resulting in a period of increased coagulation potential (20).

Firefighting activities have specifically been reported to acutely increase coagulation potential (5, 37, 39). While fire suppression activities put firefighters at risk for cardiac emergencies, lifestyle factors common amongst firefighters may also increase risk for a sudden cardiac event. Firefighting, like many other emergency-related occupations, requires prolonged shift work without adequate sleep. Bogglid et al. reported in a meta-analysis that shift work increased cardiovascular disease risk by 40% (3). To counter fatigue and disrupted sleep cycles, caffeine is commonly used (35). Shift work is associated with increased caffeine intake (4, 33), which is commonly overused among some firefighters (6). While there is some evidence for an ergogenic effect of caffeine during exercise (11), Kellawan et al. demonstrated that high caffeine intake may increase core body temperature while performing activities in PPE, increasing thermal strain, air consumption, and risk for illness among firefighters (25).

The effect of caffeine on hemostasis at rest and during exercise is not definitively known. Some studies have demonstrated *in vitro* potential for caffeine to enhance prothrombotic activity of endothelial cells (15, 34). In a recent unpublished study from our laboratory, increases in Factor VIII antigen following a maximal graded exercise test were elevated in a caffeinated versus placebo condition (1). The combination of heavy insulated PPE, strenuous physical exertion, and other physiologically stressful factors of shift work and firefighting activity present unique challenges, and the effect of caffeine on hemostasis under these conditions is unknown. Therefore, in light of the consequences cardiac emergencies pose for individual firefighters and public safety, it is important to investigate the potential effects of caffeine and firefighting activities on hemostasis and performance. It is hypothesized that caffeine intake prior to simulated firefighting activities will increase coagulation potential to a greater degree than simulated firefighting activities without caffeine supplementation.

Methods

Subjects

Twelve male firefighters participated in this study and the descriptive data for these subjects are displayed in Table 1. All participants were career firefighters with at least five years of firefighting experience to ensure familiarity with exercise in personal protective equipment (PPE) and the self-contained breathing apparatus (SCBA). Participants did not have any history of coagulation disorders and were not currently taking any medications to alter coagulation. All participants were recruited from the Harrisonburg Fire Department and were tested at the Harrisonburg Fire Department Training Grounds after obtaining informed consent. This study was approved by the Institutional Review Board of James Madison University.

Experimental protocol

Caffeine Intake: Participants were asked to report their average weekly intake of coffee, tea, chocolate, soda, and other caffeinated beverages. An approximate daily intake was obtained by assigning typical milligram doses (29) to each item. Participants were designated as having low (0 – 150 $mg\cdot day^{-1}$), moderate (151 – 300 $mg\cdot day^{-1}$), or high (>300 $mg\cdot day^{-1}$) caffeine intake based on criteria from prior studies (18).

Experimental Trials: A double-blind, randomly counterbalanced cross-over design was used. Subjects were required to abstain from caffeine, alcohol and tobacco for 24 hours, as well as fast for 10 hours prior to testing.

Supplementation: Prior to each trial, subjects ingested 500mL of either a placebo (water with non-caloric lemon flavoring) or caffeine preparation, administered in random counterbalanced order and double-blind fashion. The caffeine beverage contained 6 mg/kg body weight of anhydrous caffeine dissolved in 500 mL of water with identical lemon flavoring as the placebo. Testing was initiated one hour after supplement ingestion, with participants performing only light activities such as preparing apparatus and gear prior to testing.

Simulated Firefighting Testing: Each participant performed two trials of the simulated firefighting activities. The trials were identical except for the ingestion of either caffeine or placebo prior to the simulation test. For each subject, the two trials occurred between 9 a.m. and 11 a.m., and were separated by at least 20 days. Simulated firefighting activities were performed while wearing full PPE that is National Fire Protection Association (NFPA) 1971-compliant (Morning Pride® turnout gear, Cairns® 1010 helmet) at the Harrisonburg City Fire Training Grounds (Harrisonburg, VA). Participants also wore an MSA Firehawk SCBA with a 60-minute carbon-fiber air cylinder. The average weight of the PPE with SCBA was 29 kg. Forty-five minutes after supplement ingestion, subjects assumed a seated position for 15 minutes after which a resting venous blood sample was obtained while remaining in the seated position. Participants then donned their gear and entered the training course accompanied by a fire department safety officer. Once the simulated activity (described below) was complete, the participants immediately returned to the designated recovery area, assumed a seated position and provided post-simulated activity blood samples within two minutes of activity cessation. The time to complete the simulated activities and the change in PSI from the SCBA was also recorded.

Each participant was familiar with the course, as these testing procedures were designed for use during biannual departmental evaluations and mimic the tasks that take place during actual fire suppression duties during an emergency call. The simulated firefighting activities took place on fire training grounds that included a two-story training building surrounded by an open gravel area containing fire equipment, including two ladders, one 80 kg training dummy, one three-inch hose roll, one charged 1-3/4” hose line, a ventilation sled, five traffic cones, various tools, and a simulated ceiling-pulling station equipped with weights (Figure 1). Participants entered the simulated firefighting course at ground level, climbed up a 3.7 meter ladder to the second floor, gained entry through a window and crawled 18 meters where they reached a set of stairs. At this point, they stood up and walked down the fourteen steps to the ground level where an 80 kg training dummy was located. Subjects were required to drag the dummy 9 meters around the interior of the building, drop it at a doorway, and walk 15 meters to exit the building. Once outside, the participant picked up a roof ladder weighing 20 kg and carried it 22 meters around the exterior of the building. At the rear of the building, the ladder was be placed on the ground and a rolled section of hose (17 kg) was picked up and carried 22 meters to the front of the building. Once the hose was placed on the ground, participants walked 10 meters to the next station where they used a 4 kg rubber sledgehammer to drive a ventilation sled (72 kg) approximately 0.6 meters. Participants walked 10 meters to pick up a charged hose line, advanced forward 6 meters, opened the nozzle momentarily, closed the nozzle, and then retreated the charged line back to the starting point. After walking 25 meters to the next station, the participants alternated moving softballs and baseballs sitting on top of five traffic cones over 10 meters. Lastly, participants walked 12 meters to the simulated ceiling-pulling station where they used a pike pole to complete two sets of four pushing and four pulling motions against a 36 kg weight. The participant walked 10 meters back to the starting point and this sequence of training obstacles was then repeated, with every subject completing two full laps of the simulated firefighting activities course.

Blood sampling, assays

For the pre and post samples, 10 mL of blood was drawn from an antecubital vein. Half of this sample was drawn into an acidified citrate collection tube (Tcoag, Inc.; Mount Olive, NJ), while the other half was drawn into a normal citrate solution (Becton-Dickinson; Franklin Lakes, NJ). Samples were kept on ice during transport to the laboratory, centrifuged for 20 minutes at 4,500 x g and 4° C to obtain platelet-poor plasma, and then frozen and stored at -80° C until assayed. Plasma concentrations of Factor VIII levels, tPA activity, and PAI-1 activity were determined using commercially available ELISA kits (VisuLize® Ontario, Canada; Eagle Bioscience, Inc, Nashua, New Hampshire) according to manufacturer specifications. Plasma from samples collected in normal citrate tubes was used for Factor VIII assays, while samples from the acidified citrate collection tubes were used to assay for tPA and PAI-1 activities.

Statistical analysis

Changes in each hemostatic variable were analyzed using repeated-measure analysis of variance, with exercise (pre- and post-activity) and treatment (caffeine, placebo) as within-subjects factors. Post-hoc tests were done using paired t-tests. Paired t-tests were also used to compare time to completion of the course and air consumed during the course. Statistical significance for all analyses was set at alpha (α) = 0.05.

Results

Of the 12 subjects, six were categorized as having high habitual caffeine intake, four as moderate, and two as low. Factor VIII levels increased significantly ($P < 0.05$) from pre-exercise to post-exercise in both conditions, as shown in Figure 2. There was no main effect for caffeine supplementation on pre-exercise Factor VIII levels. However, there was a significant treatment x exercise interaction ($P < 0.05$) as Factor VIII increased more in the caffeine trial (Pre = 0.20 ± 0.13 IU/mL, Post = 0.43 ± 0.15 IU/mL) versus the placebo trial (Pre = 0.21 ± 0.11 IU/mL, Post = 0.38 ± 0.15 IU/mL). There was an effect of exercise for tPA activity, as it increased significantly ($P < 0.05$) from pre- to post-exercise in both the placebo (Pre = 0.18 ± 0.18 IU/mL, Post = 3.23 ± 3.21 IU/mL) and caffeine (Pre = 0.18 ± 0.31 IU/mL, Post = 3.97 ± 3.53 IU/mL) conditions (Figure 3). However, there was no main effect of treatment on tPA activity levels and no treatment x exercise interaction. PAI-1 activity responses are illustrated in Figure 4. There was an effect of exercise as PAI-1 activity significantly ($P < 0.05$) decreased from pre- to post-exercise in both the placebo (Pre = 33.86 ± 21.29 U/mL, Post = 28.77 ± 21.21 U/mL) and caffeine (Pre = 37.34 ± 28.81 U/mL, Post = 23.71 ± 19.42 U/mL) conditions. However, there was no main effect for treatment and no treatment x exercise interaction.

Caffeine did not significantly affect time to completion of the simulated activity course (Caffeine = 393.4 ± 37.1 seconds, Placebo = 392.4 ± 36.0 seconds). However, there was a trend ($P = 0.05$) for increased air use in the caffeinated condition (Caffeine = 1489.2 ± 145.8 psi, Placebo = 1415.8 ± 176.6 psi).

Discussion

In the present study, we observed a greater increase in Factor VIII antigen following exercise in the caffeinated condition versus the placebo condition. This occurred despite similar fibrinolytic responses in both conditions. This confirms prior data from this lab that showed larger increases in Factor VIII following maximal cycling with caffeine supplementation (1). Factor VIII is a vital part of the intrinsic pathway, which is activated during exercise-induced stimulation of coagulation. Therefore, the increase in this factor coupled with the lack of increase in fibrinolysis could have clinical significance with respect to the onset of acute coronary events. Most ischemic events, and an even greater proportion of exertion-related ischemic events, occur as a result of an occlusive thrombus (16). Furthermore, a large portion of shiftworkers, such as firefighters, overuse caffeine as an ergogenic aid on a daily basis (6, 34, 36). As the leading cause of death among firefighters is acute coronary events (13, 14), the effect caffeine has on increasing coagulation potential during firefighting activities may suggest a potential mechanism contributing to these fatalities.

While there is a paucity of data on the direct role caffeine plays in hemostasis, even fewer studies have evaluated these effects following strenuous exercise. Our lab has previously observed a treatment x exercise interaction for Factor VIII levels (1); however, data from that study also demonstrated a significant treatment x exercise interaction for tPA activity, which was not observed in the present study. Several other studies assessing the effects of caffeine on hemostasis in vitro without the added stress of exercise have observed an increase in coagulation potential (15, 35). The increase in coagulation potential combined with a lesser increase in fibrinolysis may be a potential mechanistic explanation behind the link observed between caffeine consumption and ischemic events (2, 32).

In addition, this study also confirms prior research concerning the hemostatic response to exercise. Several prior studies have shown that intense physical exertion results in an increase in coagulation, as well as fibrinolysis. Markers of coagulation such as Factor VIII, fibrinogen, prothrombin time, and partial thromboplastin time are elevated (5, 19, 20, 22, 38), while parallel increases in fibrinolytic activity occur due to increased tPA activity and depressed PAI-1 activity (7, 9, 19, 20, 31). However, other studies have shown that the increase in fibrinolysis is brief, with tPA activity returning to baseline shortly after exercise cessation, while coagulation markers remain elevated (28, 33, 38). Lin et al. assessed markers of hemostasis for 11 moderately active young men immediately after completion of a maximal cycle ergometer test. Subjects were observed to have elevated tPA activity and Factor VIII, but only Factor VIII levels remained elevated at 2-hours post-exercise whereas tPA activity had returned to baseline (28). Smith et al. also observed increased tPA activity and Factor VIII, as well as decreased PAI-1 activity immediately post-simulated firefighting; however, at 2 hours post-firefighting, tPA activity had returned to baseline while Factor VIII remained elevated and PAI-1 activity depressed (38). Thus, it is possible that the acutely larger increase in Factor VIII levels than tPA activity levels with exercise in the caffeinated condition observed in the present study persisted hours following exercise. Future studies should evaluate the effect of caffeine on hemostatic changes in the post-exercise period.

We did not observe an effect of caffeine on time to completion of the simulated activities course; however, several other studies have shown that caffeine intake has an ergogenic effect (11, 21, 42). This is proposed to be due to the alterations caffeine has on sensations of pain and force during contraction (24), which results in a lower rating of perceived exertion and prolonged exercise (11, 25). One possible explanation for this discrepancy may be that the length of the simulated firefighting activities course used in this study was too short to elicit a meaningful change in performance. In a previous meta-analysis, Doherty et al. observed that caffeine had a higher effect size with endurance exercise trials than short-term exercise (10). In the current study, the average time to completion was under 395 seconds (6 minutes, 35 seconds) in both conditions (Caffeine = 393.4 ± 37.1 seconds, Placebo = 392.4 ± 36.0 seconds); therefore, a longer activity period may be required to demonstrate caffeine performance enhancements as seen in other studies (25).

Despite the lack of observed ergogenic effect of caffeine in this study, there was a trend ($p = 0.05$) for increased air consumption in the caffeinated condition. Kellawan et al. observed a significant increase in air consumption in the caffeinated condition during submaximal treadmill walking while wearing full PPE. Caffeine has a stimulating effect on respiration, which has been observed to increase minute ventilation during submaximal and maximal exercise (8). This increase in total air consumption is of particular interest to those in the firefighting profession as the time spent performing rescues and fire suppression is limited by the air supply provided by the SCBA. The data from the current study suggest that the amount of air consumed may increase if an equivalent dose of caffeine (6 mg/kg) were ingested prior to SCBA-required activities.

Based on the calculations used by the National Institute for Occupational Safety and Health to rate the work time capacity of SCBAs for healthy male firefighters (29), the average work time for subjects in this study was reduced by approximately one minute and ten seconds in the caffeinated condition. This puts firefighters at a disadvantage when time is crucial in an immediately dangerous to life or health (IDLH) environment.

Firefighting is a unique civilian occupation requiring strenuous work performance in dangerous and stressful conditions. It is well documented that hemostatic responses to strenuous activity differ between healthy individuals and those with underlying cardiovascular disease or cardiovascular disease risk factors (44). The subjects in this study were all relatively young and healthy, and we excluded any firefighters with a known history of cardiovascular disease or those taking any medications that would alter hemostatic variables. Thus, our results may underestimate the effect caffeine may have on hemostatic disruption in firefighters with risk factors for cardiovascular disease. It should also be noted that all of the participants in this study were males, thus female firefighters may have a different hemostatic response. Another limitation of our study is the controlled environment in which the subjects performed the strenuous activity. While the activities in this study strongly resemble those performed on the fireground, the simulated course used was presented in a relaxed environment that did not involve live fire. Hence, our results did not represent the full magnitude of stressors that would be present in a true emergency and IDLH environment, both physically and psychologically. Therefore, these results could underestimate the hemostatic response to a live firefighting scenario. However, it could be anticipated that the altered hemostatic response would only be amplified in that situation. We were unable to measure the hemostatic response in the post-exercise period, however there is evidence from prior studies that the acutely significant differences in coagulation and fibrinolytic markers would be expected to persist into the post-exercise period (20, 28, 38). In addition, this study sought only to examine whether caffeine affected hemostasis, but did not assess the mechanism by which the observed effects occurred. Future research may benefit from examining the effects of caffeine on hemostatic factors during firefighting in the 1-2 hours following exertion, as well as understanding how caffeine mechanistically causes these changes.

Despite a relatively small sample size used, the findings of this study demonstrate significant hemostatic disruption in the caffeinated condition. This may provide a potential mechanism behind the high number of sudden cardiac events among firefighters. Additional research including firefighters with a wide range of cardiovascular risk profiles, more strenuous firefighting activity with live fire, a larger population, and analysis of the change in hemostatic variables in the time after firefighting activity is warranted to better understand the effects caffeine may have on the hemostatic response to firefighting.

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Table 1: Descriptive characteristics for participants

Variable	**Mean ± SD**
Age (years)	31.3 ± 5.4
Height (cm)	180.9 ± 5.1
Weight (kg)	94.2 ± 13.1
BMI (kg × m^{-2})	28.7 ± 2.9
Average Daily Caffeine Consumption (mg)	332.4 ± 215.7

The descriptive characteristics for participants (n = 12); cm=centimeters, m=meters, kg=kilograms, BMI=body mass index.

Legend for Figures

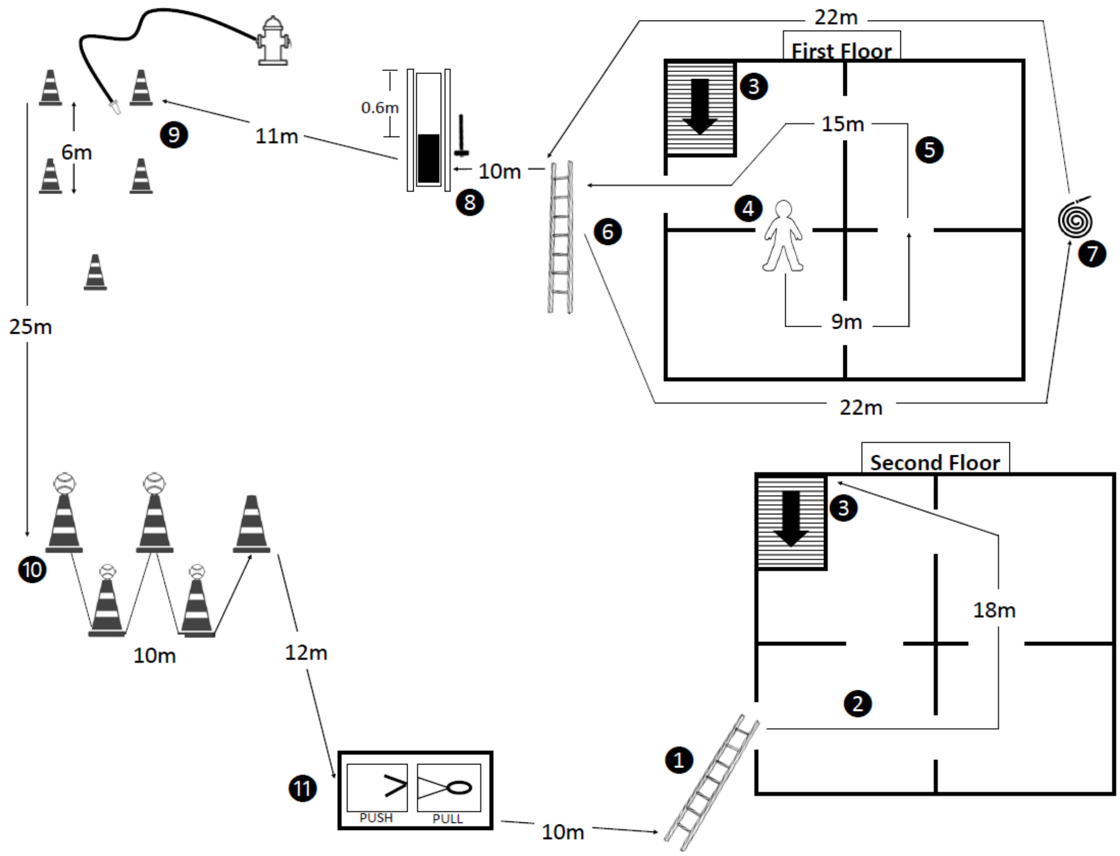
Figure 1: This diagram depicts the layout of the simulated firefighting activities course used for this study; m=meters.

Figure 2: The average Factor VIII antigen for placebo and caffeine conditions pre- and post-exercise are depicted (n = 8); Placebo (Pre = 0.21 ± 0.11 IU/mL, Post = 0.38 ± 0.15 IU/mL); Caffeine (Pre = 0.20 ± 0.13 IU/mL, Post = 0.43 ± 0.15 IU/mL). * Significant main effect of exercise (Post > Pre), ◊ indicates larger increase in the caffeine condition ($P < 0.05$)

Figure 3: The average tPA activity pre- and post-exercise in the placebo and caffeine conditions are depicted (n = 9); Placebo (Pre = 0.18 ± 0.18 IU/mL, Post = 3.23 ± 3.21 IU/mL); Caffeine (Pre = 0.18 ± 0.31 IU/mL, Post = 3.97 ± 3.53 IU/mL). * Significant main effect for exercise (Post > Pre, $P < 0.05$)

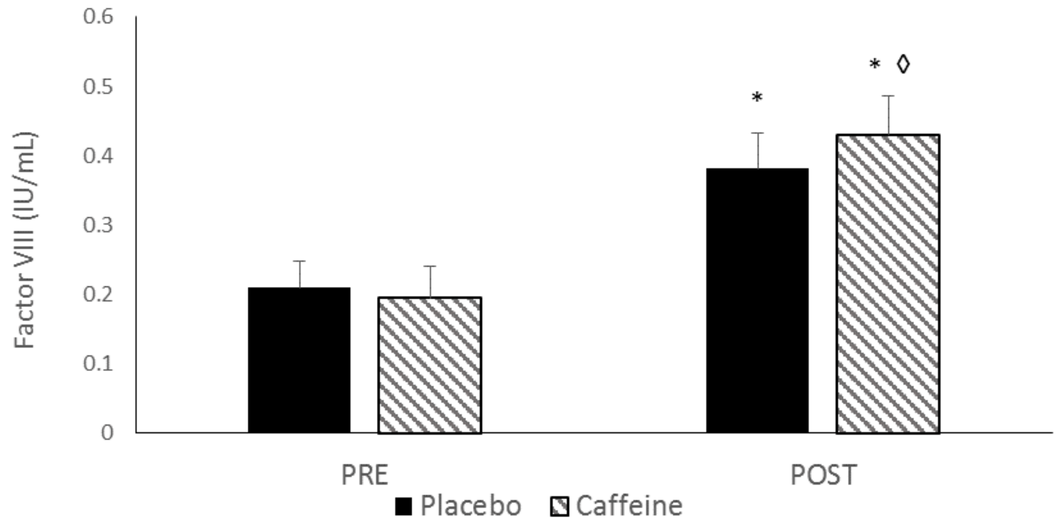
Figure 4: The average PAI-1 activity pre- and post-exercise in the placebo and caffeine conditions are depicted (n = 9); Placebo (Pre = 33.86 ± 21.29 U/mL, Post = 28.77 ± 21.21 U/mL); Caffeine (Pre = 37.34 ± 28.81 U/mL, Post = 23.71 ± 19.42 U/mL). * Significant main effect for exercise (Post < Pre, $P < 0.05$)

Figure 1: Simulated Firefighting Activities Course Diagram



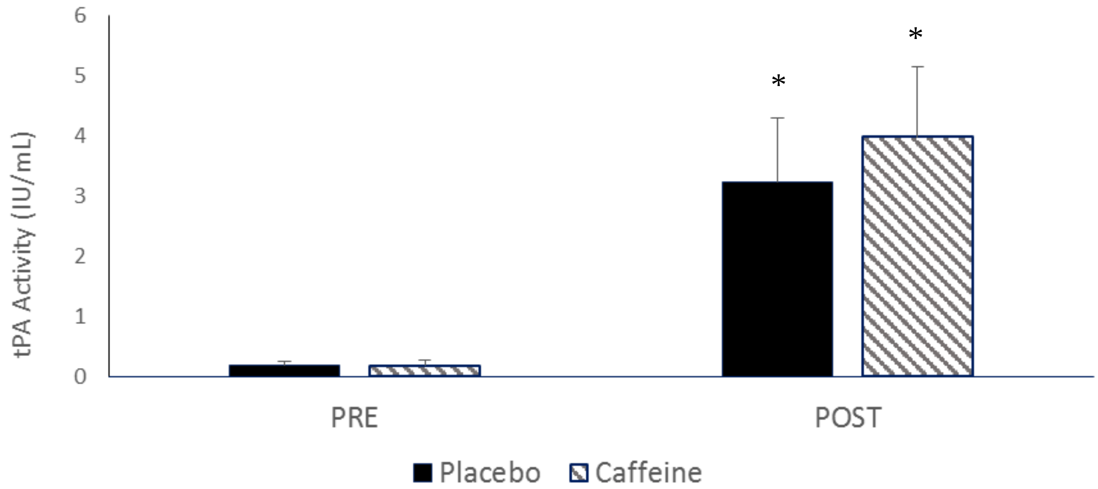
This diagram depicts the layout of the simulated firefighting activities course used for this study; m=meters.

Figure 2: Average FVIII antigen for placebo and caffeine conditions pre- and post-exercise



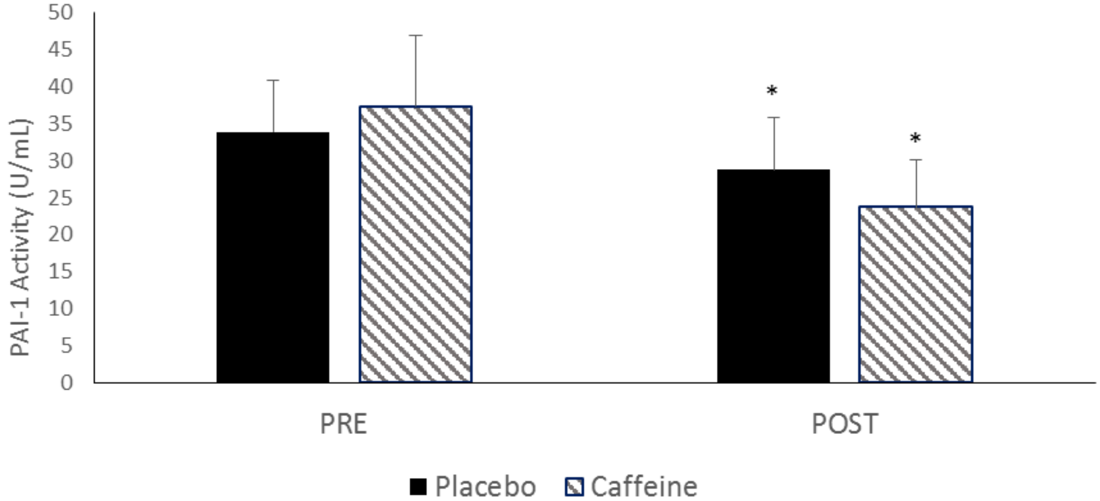
The average Factor VIII antigen for placebo and caffeine conditions pre- and post-exercise are depicted (n = 8); Placebo (Pre = 0.21 ± 0.11 IU/mL, Post = 0.38 ± 0.15 IU/mL); Caffeine (Pre = 0.20 ± 0.13 IU/mL, Post = 0.43 ± 0.15 IU/mL) *mean* ± *SD*.
* Significant main effect of exercise (Post > Pre)
◊ indicates larger increase in the caffeine condition (*P* < 0.05)

Figure 3: Average tPA activity pre- and post-exercise in the placebo and caffeine conditions



The average tPA activity pre- and post-exercise in the placebo and caffeine conditions are depicted (n = 9); Placebo (Pre = 0.18 ± 0.18 IU/mL, Post = 3.23 ± 3.21 IU/mL); Caffeine (Pre = 0.18 ± 0.31 IU/mL, Post = 3.97 ± 3.53 IU/mL) *mean* ± *SD*.
* Significant main effect for exercise (Post > Pre, $P < 0.05$)

Figure 4: Average PAI-1 activity pre- and post-exercise in the placebo and caffeine conditions



The average PAI-1 activity pre- and post-exercise in the placebo and caffeine conditions are depicted (n = 9); Placebo (Pre = 33.86 ± 21.29 U/mL, Post = 28.77 ± 21.21 U/mL); Caffeine (Pre = 37.34 ± 28.81 U/mL, Post = 23.71 ± 19.42 U/mL) *mean* ± *SD*.
* Significant main effect for exercise (Post < Pre, $P < 0.05$)

Appendix A: Consent Form

Consent to Participate in Research

Identification of Investigators & Purpose of Study

You are being asked to participate in a research study conducted by Sierra D. Wassell and Christopher J. Womack, Ph.D. from James Madison University. The purpose of this study is to determine if caffeine influences the degree to which strenuous physical activity makes your blood more prone to clot.

Potential Risks & Benefits

If you choose to participate in this study, you will perform two separate trials of simulated firefighting activities. The investigator perceives the following are possible risks arising from your participation in the study: nausea, discomfort, dizziness, and in rare occurrences, heart attack, stroke or death. The selection criteria used to obtain subjects and the "Health Status Questionnaire" are intended to mitigate these risks. In healthy individuals, the risk of death during vigorous exercise has been estimated at 1 death per year for every 18,000 individuals.

Potential benefits from participation in this study include:

Helping with research that may help determine the health impact of caffeine use for firefighters.

Research Procedures

Should you decide to participate in this research study, you will be asked to sign this consent form once all your questions have been answered to your satisfaction. This study consists of two separate trials of simulated firefighting activity. Total time for each trial is approximately 1.5 hours. All testing will occur at the Harrisonburg Fire Department Training Grounds. Furthermore, you will be asked to recall your consumption of caffeinated beverages for the previous week. You will also be subjected to blood tests both before and after each trial. Your heart rate may be monitored by a monitor that wraps around your chest.

Blood Sampling: We will obtain about 10 ml of blood prior to and immediately after post-simulated activities in order to determine the potential of your blood to coagulate. These blood samples will be obtained from an arm vein.

Confidentiality

The results of this research will be presented at conferences and published in exercise science journals. The results of this project will be coded in such a way that your identity will not be attached to the final form of this study. The researcher retains the right to use and publish non-identifiable data. However, you can ask that your data be removed from the study at any point prior to presentation and publication. While individual responses are confidential, aggregate data will be presented representing averages or generalizations about the responses as a whole. All data will be stored in a secure location accessible only to the researchers. Final aggregate results will be made available to you upon request.

Participation & Withdrawal

Your participation is entirely voluntary. You are free to choose not to participate. Should you choose to participate, you can withdraw at any time without consequences of any kind. Your right to withdraw includes the right to request that your blood samples be discarded at any time.

Questions

You may have questions or concerns during the time of your participation in this study, or after its completion. If you have any questions about the study, contact Sierra D. Wassell at wasselsd@dukes.jmu.edu, or Christopher J. Womack, Ph.D. at womackcx@jmu.edu or 540-568-6515.

Giving of Consent

I have read this consent form and I understand what is being requested of me as a participant in this study. I freely consent to participate. I have been given satisfactory answers to my questions. The investigator provided me with a copy of this form. I certify that I am at least 18 years of age.

Name of Participant (Printed)	Name of Researcher(s) (Printed)
Name of Participant (Signed)	Name of Researcher(s) (Signed)
Date	Date

For questions about your rights as a research subject, you may contact the chair of JMU's Institutional Review Board (IRB). Dr. David Cockley, (540) 568-2834, cocklede@jmu.edu.

Appendix B: Health Status Questionnaire

James Madison University
School of Kinesiology and Recreation Studies
Health Status Questionnaire

Instructions: Complete each question accurately. All information provided is **confidential.**

Part I: General Information

1. Study______________________________

2. Participant Number:
3. Gender (circle one): Male Female
4. Date of Birth (Month/Day/Year):

Part II: Medical History

5. Circle any that died of heart attack before age 50:
Father Mother Brother Sister Grandparent

6. Date of last medical exam: ______________
Last physical fitness test: ________________

7. Circle operations you have had:
Back Heart Kidney Eyes Joint Neck Ears Hernia Lung
Other__________

8. Please circle any of the following for which you have been diagnosed or treated by a physician or health professional:

Alcoholism	Diabetes	Kidney Problems
Anemia (sickle cell)	Emphysema	Mental Illness
Anemia (other)	Epilepsy	Muscular Injury
Asthma	Eye Problems	Neck Strain
Back Strain	Gout	Obesity
Bleeding trait	Hearing Loss	Orthopedic Injuries
Bronchitis, chronic	Heart Problem	Phlebitis
Cancer	High Blood Pressure	Rheumatoid arthritis
Cirrhosis, liver	Hypoglycemia	Stroke
Concussion	Hyperglycemia	Thyroid problem
Congenital defect	Infectious Mononucleosis	
	Ulcer	

Other ______________________

9. Circle all medications taken in the last six months:

Blood thinner	Epilepsy medication	Nitroglycerin
Diabetic pill	Heart-rhythm medication	Other ________________
Digitalis	High-blood pressure medication	
Diuretic	Insulin	

10. Any of these health symptoms that occur frequently is the basis for medical attention. Circle the number indicating how often you have each of the following:

5 = Very often 4 = Fairly often 3 = Sometimes 2 = Infrequently 1= Practically never

a. cough up blood 1 2 3 4 5	f. chest pain 1 2 3 4 5
b. abdominal pain 1 2 3 4 5	g. swollen joints 1 2 3 4 5
c. low back pain 1 2 3 4 5	h. feel faint 1 2 3 4 5
d. leg pain 1 2 3 4 5	i. dizziness 1 2 3 4 5
e. arm or shoulder pain 1 2 3 4 5	j. breathless on slight exertion 1 2 3 4 5

Part III: Health Related Behavior

11. Do you smoke? Yes No

12. If you are a smoker, indicate the number of smoked per day:

Cigarettes: 40 or more 20-39 10-19 1-9

Cigars or pipes only: 5 or more or any inhaled less than 5, none inhaled

13. Do you exercise regularly? Yes No

14. How many times in a week do you spend at least 30 minutes in moderate to strenuous/vigorous exercise?

1 2 3 4 5 6 7 days per week

15. Can you walk 4 miles briskly without fatigue? Yes No

16. Can you jog 3 miles continuously at a moderate pace without discomfort?
Yes No

17. Weight now: ___________ lbs.
One year ago: ___________ lbs.
Age 21: ___________ lbs.

18. How long have you been actively involved in firefighting activities?
< 1 year 1-5 yrs 5-10 yrs 10-15 yrs >15 yrs

Appendix C: Caffeine Habits Questionnaire

Caffeine Habits Questionnaire

Please list your approximate WEEKLY intake of the following:

- Cups of coffee (8 oz):

- Cups of tea (8 oz):

- Cans (12 oz) of caffeinated soda:

- Cans of energy drinks (please specify size of can in ounces):

- Servings of chocolate:

- Doses of caffeinated pills (No-Doz, Vivarin, etc.):

- Other caffeinated beverages not listed (please list specific drink and weekly intake):

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