The Effects of Caffeine Ingestion on Firefighter Work Tolerance

by

Jeremy Mikhail Kellawan
Bachelor of Science, University of Guelph, 2005

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of the Requirements for the Degree of

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in Kinesiology in the School of Exercise Science, Physical & Health Education

University of Victoria

Supervisory Committee

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Abstract

Anecdotal evidence suggests that caffeine ingestion (mostly in the forms of coffee and tea consumption) is prevalent amongst firefighters and yet there is no data on whether this behaviour should be identified, measured, or monitored. PURPOSE: The purpose of this experiment was to determine the physiological and psychophysical effects of caffeine ingestion during repeated bouts of simulated firefighter work. In a randomized, double blind, crossover design, ten healthy males (age 36 ± 9.8 yr, body mass 88.3 ± 5.7 kg, height 182.78 ± 3.9 cm, approximate caffeine use 492.8 ± 318.2 mg/day) completed three 10 min work bouts (WB) at an intensity one work load below ventilatory threshold wearing full Firefighter personal protective equipment (PPE) and breathing through a self contained breathing apparatus (SCBA) on two different occasions. One hour before exercise each subject ingested either a 6 $mg \cdot kg^{-1}$ of caffeine (CAFF) or dextrose placebo (PLA), as well as, 500 ml of water. During the work trials, expired gases were sampled for oxygen consumption ($\dot{V}O_2$), carbon dioxide production

($\dot{V}CO_2$), respiratory exchange ratio (RER), minute ventilation ($\dot{V}_E$), respiratory rate (RR), tidal volume (V_t), and total air consumed (AcV_E). Core temperature (T_c), heart rate (HR), oxyhemoglobin saturation (% O_2 sat), capillarized blood lactate (BLa), rating of perceived exertion (RPE) (10pt Borg), perceived thermal distress (PTD), and sweat loss were also measured. Physiological strain index (PSI) was calculated from HR and T_c values. T_c was significantly higher in all CAFF WB compared to PLA ($37.83 \pm 0.08\ ^oC$ vs. $37.61 \pm 0.12\ ^oC$) ($p \leq 0.05$). $\dot{V}_E$ and V_t were also significantly increased in CAFF whereas, RPE was significantly decreased ($p \leq 0.05$). The elevated T_c values caused an increase in calculated PSI in the CAFF condition during exercise ($p \leq 0.01$). CAFF increases in $\dot{V}_E$ and V_t also increased AcV_E. In conclusion, a caffeine induced elevation in T_c caused increased strain as indicated by calculated PSI during repeated work bouts during exercise below ventilatory threshold wearing full PPE and breathing through an SCBA. Elevated T_c in the CAFF condition likely caused increases in $\dot{V}_E$, V_t and AcV_E. Thus, caffeine ingestion may have to be monitored in firefighters during work days.

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Dedication

To my grandmothers Eileen Kellawan, Margaret Semple and to my grandfathers Campbell Semple, and Ronald Kellawan

Introduction

Caffeine is the most widely distributed and consumed pharmaceutical in the world, and has been extensively researched by exercise physiologists due to its ergogenic properties (Fredholm, Battig, Holmen, Nehlig, & Zvartau, 1999; Graham, 2001). Caffeine ingestion has been shown to delay exhaustion, alter the perception of fatigue, and improve exercise performance and work tolerance with no negative effect on fluid balance (Armstrong, 2002; Armstrong, Pumerantz, Roti, Judelson, Watson, & Dias, 2005; Doherty, 2004b; Doherty & Smith, 2005; Graham, 2001; Maughan, 2003). Most research involving caffeine and exercise in heat stress apply environmental heat and humidity during exercise modalities of running or cycling in normal exercise attire of shorts and t-shirt.

The micro-climate created by the personal protective equipment (PPE) worn by firefighters and the resistance to breathing caused by a self-contained breathing apparatus (SCBA) are unique stresses in which the effect of caffeine on work tolerance is unknown. The micro-climate of PPE applies a distinctive heat stress by impeding the exchange of metabolic heat from the body into the atmosphere, thus increasing the risk of heat illness and injury when compared to most other occupations (Baker, 2000; Smith, 2001).

Caffeine ingestion under heat stress while wearing normal exercise attire does not cause increases in rectal or tympanic temperature, however, an increase in heart rate (HR), blood lactate, and blood pressure (BP) have been observed when compared to placebo (Cohen, 1996; Stebbins, 2001). Therefore, caffeine may have negative effects causing increases in HR and BP during heat stress without increased demand of work producing additional stress on the cardiovascular and thermoregulatory systems.

Furthermore, artificial increases in HR and lactate may lead to premature fatigue during exercise by causing an individual to reach maximum HR sooner and decreasing their blood pH to a fatiguing level (Astrand, Rodahl, Dahl, & Stromme, 2003).

Conversely, the ergogenic effects of caffeine may improve firefighter performance by allowing emergency scenarios to be completed in a more timely fashion. Caffeine is a known respiratory stimulant that augments ventilation under exercise conditions (Doherty & Smith, 2005). The mechanisms underlying changes in ventilation are unknown, however it has been speculated that caffeine increases the efficiency of the ventilatory volume (Doherty & Smith, 2005). The respiratory stimulatory action of caffeine could potentially ease the work of breathing through the SCBA.

There is an 18% reduction in $\dot{V}O_{2max}$ during exercise while wearing PPE and breathing through an SCBA (Dreger, 2006). The resistance to breathing caused by the SCBA has been implicated to decrease $\dot{V}O_{2max}$ by altering alveolar ventilation (observed by an increase in minute ventilation ($\dot{V}_E$), reduction of tidal volume, and gas exchange) and oxyhemoglobin saturation (Dreger, 2006). It is important to note that the external breathing resistance imposed by the SCBA appears to only influence $\dot{V}_E$ at ventilations in the 80-100 $L \cdot min^{-1}$ range (Eves, Petersen, & Jones, 2003a; Eves, Petersen, & Jones, 2003b; Eves, Jones, & Petersen, 2005).

In contrast, during treadmill exercise (mouth breathing) at 50% $\dot{V}O_{2max}$, 3.3 $mg \cdot kg^{-1}$ of caffeine ingestion has been found to increase alveolar ventilation (calculated from physiological dead space ventilation) by 12.2% (Brown, Knowlton, Sullivan, & Sanjabi, 1991). Ingestion of caffeine has also been shown to significantly reduce the slow component of $\dot{V}$ O_2 in well-trained runners exercising at 90% $\dot{V}$ O_{2max} which corresponded to a reduction in ventilation (Santalla, 2001). The ability of caffeine to alter the work of breathing could potentially improve the work tolerance of firefighters while breathing through a SCBA by limiting the reductions in alveolar ventilation and O_2 saturation associated with the SCBA.

Improved breathing efficiency may also explain reduced rating of perceived exertion (RPE) values observed in most exercise studies with caffeine ingestion (Doherty & Smith, 2005). Metabolic cost ($V0_2$) of work has been suggested to be the most important determinant of RPE (Noble & Robertson, 1996). A more efficient respiratory system may facilitate an enhanced blood flow to the working muscle which could lead to both an enhancement of performance and reduction of RPE with caffeine ingestion.

In addition to thermoregulatory, cardiovascular, and ventilatory actions, caffeine is a compound that has multiple effects on the body during exercise, all of which could potentially affect the work tolerance of firefighters working in PPE and using a SCBA. The ergogenic actions of caffeine have been implicated to enhance exercise performance by also modulating metabolic and neurological variables. More directly caffeine has been implicated in altering motor recruitment of muscle fibers, perception of pain/discomfort, delivery of substrates (i.e. fatty acids), altering carbohydrate and fat metabolism, as well as, improving the excitation-contraction coupling of skeletal muscle (Davis, 2003; Farag, 2005; Graham & Spriet, 1995; Graham, 2001; James, 2005; Kalmar, 1999; Kalmar, 2005; Lindinger, Willmets, & Hawke, 1996; Mohr, 1998; Rauh, 2006). The overall systemic effect of caffeine seems to be small alterations in several different exercise variables that manifests as an overall improvement in performance.

Anecdotal evidence suggests that caffeine ingestion (mostly in the forms of coffee and tea consumption) is prevalent amongst firefighters and yet, there are no data on whether this behaviour should be monitored, controlled, or encouraged. This study could provide reason for developing such criteria through the description of the physiological responses to repeated work bouts after caffeine ingestion while wearing PPE and SCBA breathing.

PURPOSE: The purpose of this experiment was to determine the physiological and psychophysical effects of caffeine ingestion during repeated bouts of simulated firefighter work.

Delimitations

1. Firefighters (professional or volunteer, with at least 1 year of experience) or subjects familiar to exercise with PPE and SCBA breathing.
2. Age 20-50 years; Successful response to Physical Activity Readiness Questionnaire (PAR-Q) and successful response to GI condition questionnaire.
3. Habitual (at least 1 cup of coffee/tea etc. per day) caffeine user.

Limitations

No measurement of plasma caffeine or dimethylxanthine concentration.

Measurements of perceived exertion and thermal distress are purely subjective.

Only capillarized blood was sampled.

Experimental trials were terminated if a volunteer’s core temperature reaches 39.5° C; therefore, trials may end before 30 min of work is completed.

Pure caffeine has a greater ergogenic effect than coffee (Graham, 2001).

Assumptions

The participants provided maximal effort during preliminary testing and experimental trials.

Participants adhered to the pre-test guidelines.

There will be no learning effect between trials.

The placebo will properly blind subjects.

6 $mg \cdot kg^{-1}$ of pure caffeine elicits a plasma concentration of ~40 µM (Graham & Spriet, 1995).

Maximum plasma concentration of caffeine is reached 60 min post ingestion and is maintained during exercise up to 60 min (Graham & Spriet, 1995).

Heat stress and dehydration does not alter pharmacokinetics of caffeine (McLean, 2002).

Caffeine interacts with all target tissues (central and peripheral nervous system, skeletal muscle) (Lindinger et al., 1996; Mohr, 1998; Soto, Sacristan, & Alsar, 1994).

Sweat loss will be determined by changes in body mass after exercise under the assumption that loss of body mass is due to sweat (nude body mass before- nude body mass after).

Research Questions

1. Does caffeine beneficially alter ventilatory and/or cardiovascular responses during sub-ventilatory threshold repeated work bouts while breathing through an SCBA and wearing firefighter personal protective equipment allowing for greater work tolerance when compared to a placebo?

2. Does caffeine beneficially alter core temperature during sub-ventilatory threshold repeated work bouts while breathing through an SCBA and wearing firefighter personal protective equipment allowing for greater work tolerance when compared to placebo?

3. Does caffeine beneficially alter psychophysical variables during sub-ventilatory threshold work below while breathing through an SCBA and wearing firefighter personal protective equipment allowing for greater work tolerance when compared to placebo?

Hypotheses

Caffeine will not cause a significantly different physiological and perceptual response during 3 repeated work bouts separated by 5 minutes of active recovery at a work rate equivalent to one work load below ventilatory threshold while breathing through an SCBA and wearing firefighter protective equipment when compared to placebo. No change will be seen in core temperature, in addition, no beneficial responses in ventilatory and perceptual variables will be observed nor negative cardiovascular changes leading to no overall change in work tolerance.

Definition of Terms

Work Tolerance: Ability to tolerate work as indicated by the physiological response to exercise in PPE

Core Temperature: refers to the internal temperature (^oC) of the body as measured by "Jonah" core temperature capsule and with VitalSense integrated physiological monitoring system.

Physiological strain index: Calculated index based on T_c and HR that quantifies the strain of thermoregulatory and cardiovascular systems on a scale from 0-10 (0= no stress, 10= Very high stress) (Moran, Montain, & Pandolf, 1998).

PPE: Firefighter personal protective equipment

SCBA: Self Contained Breathing Apparatus. Participants breathed through a modified regulator that allows expired air to be sampled. The regulator was connected to a protective mask worn by the participants and breathing normoxic air (21% O_2) from K-cylinders located next to the treadmill. Participants also carried a full personal compressed air bottle pack during exercise.

Work Bout (WB) or VT-1: Refers to work loads, 10 minutes in duration at an intensity equal to one work load below ventilatory threshold.

Methods

Participants

Ten participants (six urban firefighters recruited from the greater Victoria area and four non firefighters) volunteered for the study. All participants were familiar to exercise in PPE and breathing with the SCBA. The participants had a mean 6.8 ± 6.8 years of professional or volunteer firefighting experience. The age of the participants ranged from 24-48 yrs (36 ± 9.8), body mass was 88.3 ± 5.7 kg, and height was 182.78 ± 3.9 cm. The participants average caffeine use was 4.4 ± 2.5 cups of coffee or tea per day. That would elicit an approximate 492.8 ± 318.2 mg of caffeine per day (Fredholm et al., 1999). All procedures were explained and each subject provided written informed consent to participate. This project was approved by the University of Victoria human research ethics board and biosafety committee.

Table 1: Participant Characteristics

Characteristic	Mean	SD	Range
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	33.65	3.05	39.47-30.62
Body mass (kg)	88.31	5.74	99-76.6
VT ($ml \cdot kg^{-1} \cdot min^{-1}$)	25.56	1.98	30.41-23.41
Height (cm)	182.77	3.87	188-175

Note: Values are reported as means ± standard deviation. $\dot{V}O_{2peak}$ is oxygen uptake and normalized to total mass of participants in full PPE. (n=10)

Experimental design

A double-blind repeated-measures experimental design was used. Each participant performed one graded exercise test (GXT) and two experimental exercise trials. The order of the experimental trials was randomly assigned in a crossover design to prevent an order effect. One trial consisted of a participant ingesting a bolus of caffeine (6 $mg \cdot kg^{-1}$) (CAFF) while the other trial consisted of ingestion of a dextrose placebo (PLA). All trials were separated by at least 24 hours.

Determination of Ventilatory Threshold

Before participating in the experimental trials, each participant completed an incremental treadmill test to exhaustion to determine their peak level of oxygen consumption ($\dot{V}O_{2peak}$) and ventilatory threshold (VT). Height and nude body weight were also recorded. Each participant was reweighed once wearing full PPE (pants, jacket, protective face mask, anti-flash hood, helmet and gloves), heart rate monitor (Polar, Finland) and SCBA. The incremental test consisted of the participant walking at a speed of 3.5 mph with grade increasing 2% every 2 min until VT was reached. Work loads were then lowered to 1 min duration. If the participant reached a 16% grade, the speed was increased by 0.5 mph each work load until exhaustion. Termination of the test was at volitional fatigue. After cessation of the test, PPE was removed and the participant completed a 5 min cool down at 0% grade and 2.5 mph.

Gas analysis was conducted by sampling expired air during the exercise using a metabolic cart (Parvomedics, USA). The metabolic cart was calibrated using gases of known concentrations and the volume sensor was calibrated with a 3 L calibration syringe. The participant's $\dot{V}O_{2peak}$ value was considered to be the highest VO_2 (volume of oxygen consumed) achieved over 20 s during the last work increment completed. Ventilatory threshold was considered to be the point where $\dot{V}_E/\dot{V}O_2$ ratio increased while $\dot{V}_E/\dot{V}CO_2$ remained relatively constant (Eves et al., 2005; Wasserman, 1987).

Experimental Procedures

Each experimental trial consisted of 3 work bouts, 10 min in duration of treadmill walking at an intensity equivalent to one work load below VT (VT-1). Each work bout was separated by 5 min of active recovery at 0% grade and 2.5 mph. During the recovery, only the SCBA regulator was removed and the subject breathed room air. The participant consumed either 6 $mg \cdot kg^{-1}$ of caffeine or a placebo. The laboratory was kept at an ambient temperature between 21-25 ^{o}C. The participant was not allowed to drink water during the experimental trial.

Each participant reported to the laboratory without partaking in physical activity, drinking alcohol or consuming caffeine in the previous 24 hours. They were instructed to hydrate 24 hours before participating in any of the trials and to maintain the same level of hydration prior to all trials.

Upon arrival at the laboratory the participant's nude body mass was recorded and urine specific gravity (Usg) was measured with a pocket refractometer (Atago Inc, USA) to monitor hydration status. Each participant ingested an activated Jonah core temperature capsule (Mini Mitter Company Inc., USA) and the experimental bolus of either CAFF or PLA. Following ingestion, the participant was given 60 min of rest and ingested 500ml of water during the rest period. After the rest period the participant dressed in full firefighter personal protective equipment (PPE), protective mask and SCBA with a modified regulator that allows expired air to be sampled.

Perception of Work

During every 10 min work bout the participant was asked to give a rating of perceived exertion (RPE) (10 pt modified Borg scale) (appendix B) and 9 pt perceived thermal distress (PTD) (appendix C) scale at minutes 1, 5, and 10 (Burdon, Juniper, Killian, Hargreave, & Campbell, 1982).

Sweat Loss

Immediately after completion of all 3 work bouts and cool down, the participant towelled dry and their nude body mass was recorded. Determination of sweat loss was determined by changes in body mass after exercise under the assumption that loss of body mass is due to sweat (nude body mass before- nude body mass after).

Blood Sampling and Analysis

Blood was sampled during exercise at minutes 1, 5, and 10. Capillarized blood was drawn via a finger prick from an auto lancet and analyzed for blood lactate using a blood lactate test meter (Lactate Pro, Arkray Inc., Japan).

Body temperature

Core temperature (T_c) was monitored with VitalSense intergraded physiological monitoring system (Mini Milter Company Inc., USA). T_c was directly measured by telemetry from the ingested Jonah core temperature capsules and was recorded every minute.

Heart Rate

Heart rate (HR) was continuously sampled by telemetry with a heart rate monitor (Polar, Finland).

Oxyhemoglobin saturation

Oxyhemoglobin saturation was measured by pulse oximetry every 2 min (Criticare Systems Inc, USA) (Eves et al., 2005).

Calculation of Physiological Strain index

Physiological strain index (PSI) was calculated from HR and T_c. PSI = $5(T_{ct} - T_{c0}) \times (39.5 - T_{c0})^{-1} + 5(HR_t - HR_0) \times (180 - HR_0)^{-1}$ (Moran et al., 1998). T_{ct} is core temperature and HR_t is heart rate at one point. And T_{c0}, HR_0 are initial values (HR_0 was placebo values and used in the calculation for both CAFF and PLA trials).

Ventilatory Variables

Ventilatory measurements were taken as 1 min averages during the three 10 min work bouts. Inspired and expired gas measurements and equipment calibration was the same as described above in initial testing. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, respiratory rate (RR), V_t (tidal volume), RER, and total air consumed (AcV_E), was calculated by computer software (Parvomedics, USA). The participant was connected to the metabolic cart via a modified regulator that allows sampling of expired air from the SCBA.

Statistical Analysis

Factorial repeated measures analysis of variance (ANOVA) was conducted to detect significance among and within treatments on continuously sampled variables. Significant differences were established using a Tukey post hoc test. If necessary, a dependent t test was used for comparison of pre/post test variables in different conditions. Statistical significance was set to $p < 0.05$.

Results

Hydration Status

There was no significant difference in the urine specific gravity (USG) between placebo (1.014 ± 0.003) and caffeine (1.006 ± 0.002) trials ($p \geq 0.05$). Similarly, there were no differences discovered between placebo (1.08 ± 0.14 kg) and caffeine (1.28 ± 0.14 kg) in body mass sweat losses ($p \geq 0.05$).

Ventilatory & Cardiovascular Variables

$\dot{V}O_2$, $\dot{V}CO_2$, and RR were not different between placebo and caffeine conditions ($p \geq 0.05$). However, within each condition $\dot{V}CO_2$ and RR did significantly increase with time and with each work bout (Table 2) ($p \leq 0.05$). Within each condition $\dot{V}_E$ and V_t did significantly increase, however, caffeine significantly increased $\dot{V}_E$ and V_t over the placebo (Table 2) (Effect size [ES] $\dot{V}_E\ r = 0.34$, $V_t\ r = 0.49$) . Likewise, total air consumed was greater after caffeine ingestion (2072.34 ±41.10 L) when compared to placebo (1964.45 ± 41.00 L) (Figure 1) (ES, $r = 0.80$). Caffeine also increased air consumed in both work bouts 2 and 3 (Figure 1). Oxyhemoglobin saturation (%) was not altered by caffeine. HR was unaffected by caffeine treatment but in both conditions, increased over time and with each work bout ($p \leq 0.05$).

Metabolism

Capillarized blood lactate concentration was unaltered by CAFF and was not different between work bouts or over time (Table 3). Differences in RER were also not significant between caffeine and placebo, however within each condition RER did increase over time and between work bouts ($p \leq 0.05$) (Table 3).

Psycho-Physiological

The only psycho-physiological to be altered by CAFF was rating of perceived exertion (RPE) which was lowered ($p \leq 0.05$) (ES, $r = -0.46$). RPE and perceived thermal distress (PTD) both significant increased within each condition between work bouts (Table 4).

Core Temperature and Physiological Strain Index

As shown in Figure 2, core temperature was significantly elevated by caffeine ($p \leq 0.05$) (ES, $r = 0.74$). Caffeine also elicited a significantly increased core temperature over time and during each work bout (Figure 2) ($p \leq 0.01$). Physiological strain significantly increased with each work bout and over time in each condition; these values were also higher in the caffeine condition when compared to placebo ($p \leq 0.01$) (Figure 3) (ES, $r = 0.60$).

Table 2: Cardiovascular and Respiratory responses to three 10 min WB at VT-1 in full firefighter PPE and breathing through an SCBA after ingestion of 6 mg· kg^{-1} caffeine or placebo

Variable	Placebo				Caffeine			
	Work Bout #1	Work Bout #2	Work Bout #3	Overall	Work Bout #1	Work Bout #2	Work Bout #3	Overall
$\dot{V}$ O_2 (ml·kg^{-1}·min^{-1})	22.15 ±0.88	22.11 ±0.98	22.21 ±1.10	22.16 ±0.98	22.62 ±0.89	22.42 ±0.99	22.85 ±1.02	22.63 ±0.98
$\dot{V}_E$ (L·min^{-1})	56.05 ±2.49	61.94 ±3.41	67.46 ±3.33	61.82 ±3.08	59.79 ±2.23	64.03 ±3.21	71.23 ±3.81	65.02* ±3.08
$\dot{V}$ CO_2 (L·min^{-1})	2.38 ±0.08	2.43 ±0.09	2.48 ±0.09	2.43 ±0.09	2.45 ±0.08	2.46 ±0.10	2.58 ±0.10	2.50 ±0.09
V_t (L)	2.53 ±0.10	2.65 ±0.15	2.71 ±0.12	2.60 ±0.13	2.70 ±0.11	2.74 ±0.12	2.80 ±0.18	2.74* ±0.13
RR (Breaths·min^{-1})	27 ±1	29 ±1	31 ±1	29 ±1	27 ±1	28 ±1	31 ±1	29 ±1
O_2 Sat. (%)	97 ±1	97 ±1	97 ±1	97 ±1	98 ±1	99 ±1	97 ±1	98 ±1
HR (beats·min^{-1})	140 ±3	152 ±4	165 ±3	153 ±3	137 ±3	153 ±3	168 ±4	153 ±4

Note: Values are reported as means ± standard errors. $\dot{V}$ O_2 is oxygen uptake and normalized to total mass of participants in full PPE. $\dot{V}_E$, minute ventilation; $\dot{V}$ CO_2, volume of CO_2 produced; V_t, tidal volume; RR, respiratory rate; O_2 sat, oxyhemaglobin saturation; HR, heart rate

* Significant difference between placebo and caffeine conditions

Table 3: Metabolic responses to three 10 min WB at VT-1 in full firefighter PPE and breathing through an SCBA after ingestion of 6 mg· kg^{-1} caffeine or placebo

Variable	Placebo				Caffeine			
	Work Bout #1	Work Bout #2	Work Bout #3	Overall	Work Bout #1	Work Bout #2	Work Bout #3	Overall
RER	1.02 ±0.03	1.05 ±0.04	1.07 ±0.04	1.05 ±0.04	1.02 ±0.03	1.04 ±0.03	1.06 ±0.04	1.04 ±0.03
BLa (mmol/l)	3.05 ±0.50	3.00 ±0.80	3.38 ±0.72	3.15 ±0.67	2.94 ±0.80	3.44 ±0.62	3.87 ±0.52	3.42 ±0.97

Note: Values are reported as means ± standard errors. RER, respiratory exchange ratio; BLa, capillarized blood lactate

* Significant difference between placebo and caffeine conditions

Table 4: Psycho-Physiological responses to three 10 min WB at VT-1 in full firefighter PPE and breathing through an SCBA after ingestion of 6 mg· kg^{-1} caffeine or placebo

Variable	Placebo				Caffeine			
	Work Bout #1	Work Bout #2	Work Bout #3	Overall	Work Bout #1	Work Bout #2	Work Bout #3	Overall
RPE	2.87 ±0.30	3.85 ±0.37	5.25 ±0.58	3.99 ±0.42	2.43 ±0.19	3.38 ±0.39	4.85 ±0.65	3.56* ±0.41
PTD	3.22 ±0.31	4.42 ±0.46	5.70 ±0.50	4.44 ±0.43	2.70 ±0.19	4.05 ±0.40	5.20 ±0.49	3.98 ±0.36

Note: Values are reported as means ± standard errors. RPE, rating of perceived exertion; PTD, perceived thermal distress;

* Significant difference between placebo and caffeine conditions

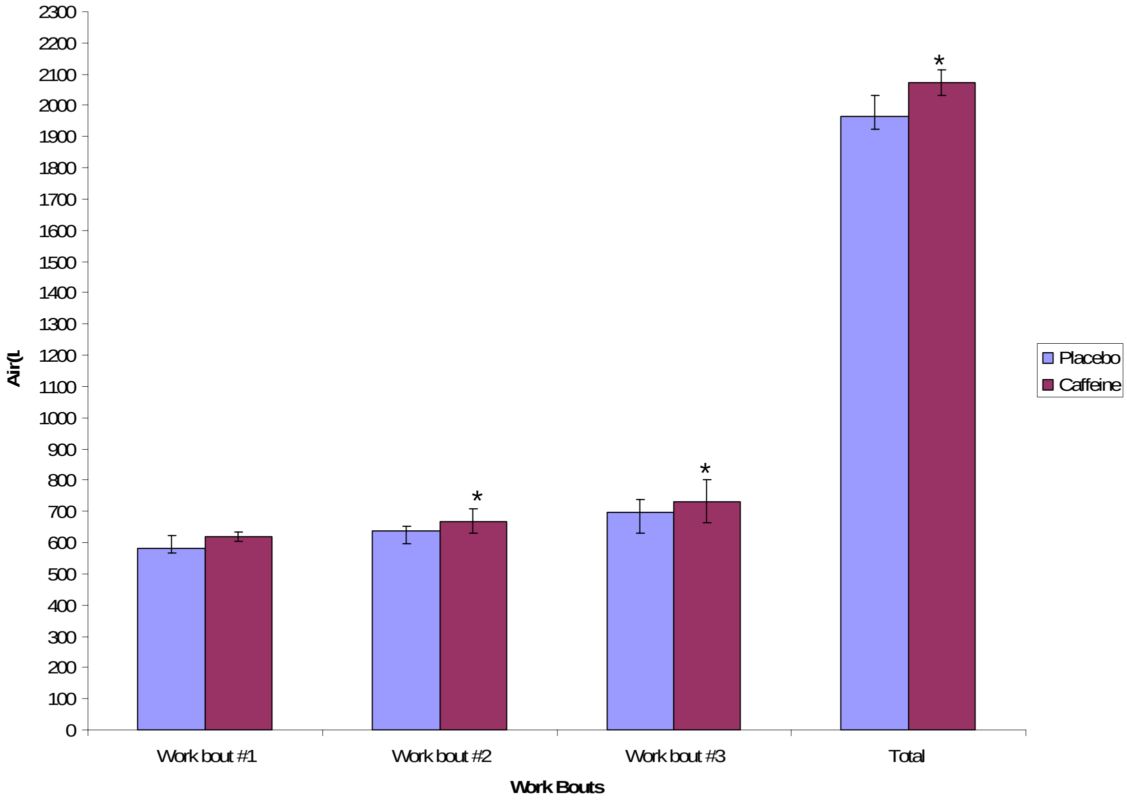

Figure 1. Volume of air consumed during 10 min WB at VT-1 in full firefighter PPE and breathing through an SCBA after ingestion of 6 mg·kg^{-1} of caffeine or placebo

Note: Values are reported as means ± standard errors
* Significant difference between caffeine and placebo conditions ($p \leq 0.05$)

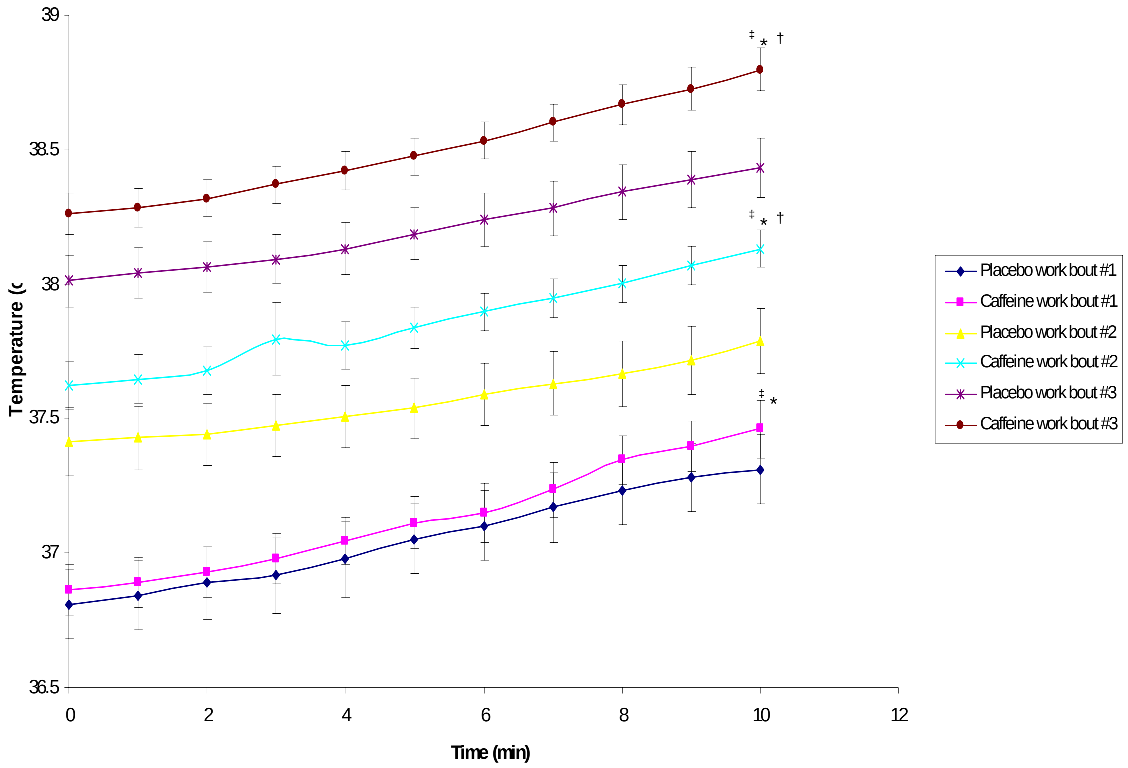

Figure 2. Core Temperature during three 10 minute WB at VT-1 wearing full firefighter PPE and breathing through an SCBA after ingestion of 6 mg·kg^{-1} of caffeine or placebo (n = 9)

Note: Values are means ±standard errors
† Significant difference between caffeine and placebo during a Work bout
‡ Significant difference between caffeine and placebo over time during a work bout
* Significant overall difference between caffeine and placebo (p ≤ 0.05)

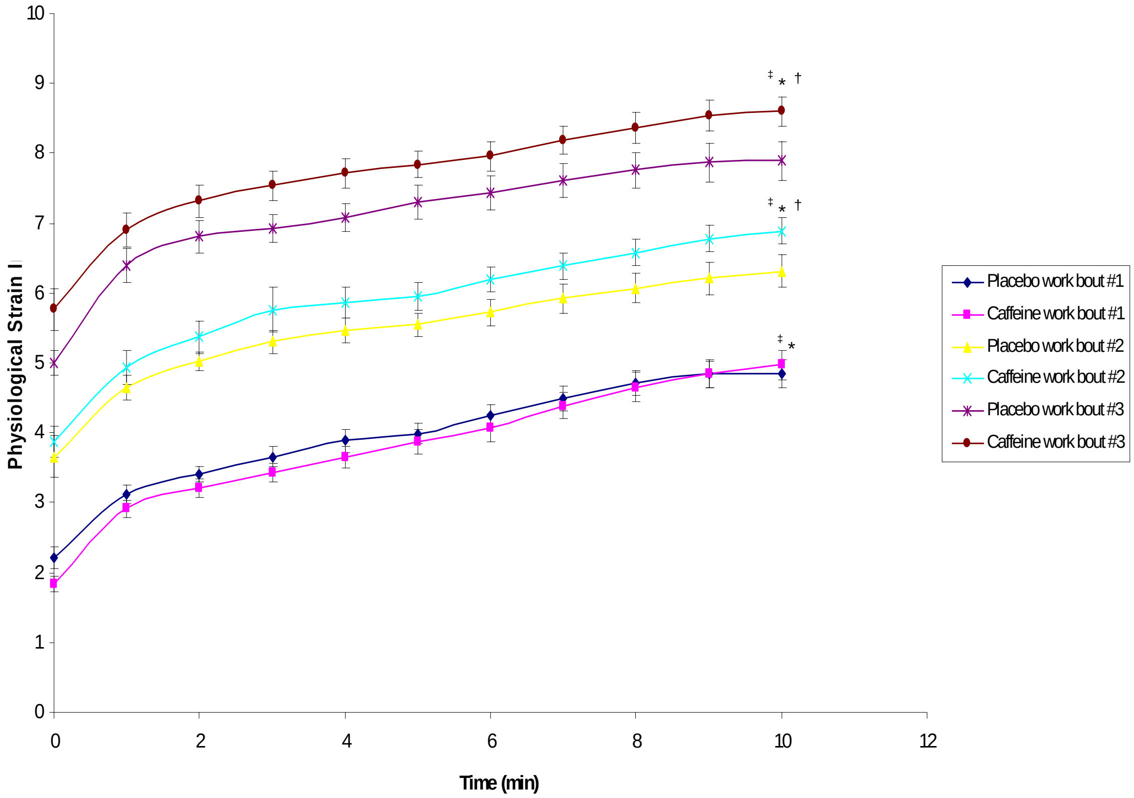

*Figure 3***.** Calculated Physiological strain during three 10 minute WB at VT-1 wearing full firefighter PPE and breathing through an SCBA after ingestion of 6 mg·kg^{-1} of caffeine or placebo (n = 9).

NOTE: PSI = $5(T_{ct} – T_{c0}) \times (39.5- T_{c0})^{-1} + 5 (HR_t – HR_0) \times (180- HR_0)^{-1}$ (Moran et al., 1998). T_{ct} is core temperature and HR_t is heart rate at anytime. And $T_{c0,}$ HR_0 are initial values. Values are means ± standard errors

† Significant difference between caffeine and placebo during a Work bout

‡ Significant difference between caffeine and placebo over time during a work bout

* Significant overall difference between caffeine and placebo ($p \leq 0.05$)

Discussion

Ventilatory Variables

Firefighting is a unique occupation that introduces distinctive physiological challenges on the body. The weight of equipment and its effect on efficiency of exercise and work tolerance have been shown to elicit higher submaximal $\dot{V}O_2$, $\dot{V}_E$, and HR when compared to regular exercise conditions (Dreger, 2006; Eves, Petersen, & Jones, 2003b). Although, the exact cause of $\dot{V}_E$ limitation by PPE and SCBA is unknown, recent research indicates that an increased work of breathing due to expiratory resistance caused by the regulator in combination with impairment in thoracic excursions due to the weight of the SCBA harness are the leading factors (Dreger, 2006).

The results of the current study revealed that caffeine does not alter $\dot{V}O_2$, $\dot{V}CO_2$, and RR during three 10 min work bouts (WB) at an intensity one work level below ventilatory threshold (VT-1) in full firefighter PPE and breathing through an SCBA (Table 2). However, caffeine significantly increased $\dot{V}_E$ and V_t during the same conditions. Increases in $\dot{V}_E$ and V_t without a difference in RR and/or $\dot{V}O_2$ suggest that caffeine was not able to ease the work of breathing that is associated with exercise in PPE and SCBA breathing. Increased $\dot{V}_E$ and V_t without proportional increases in RR indicate that participants were able to uptake and expel more air per breath in the CAFF condition when compared to PLA.

Caffeine is a known respiratory stimulant that augments ventilation under exercise conditions (Doherty & Smith, 2005). In an experiment that evaluated the effect of caffeine on loading breathing, caffeine increased time to exhaustion and decreased the decay of centroid frequency EMG of the diaphragm at all resistances tested (Supinski, Levin, & Kelsen, 1986). Caffeine has been implicated to improve central recruitment and increase contractility (via increased intracellular Ca^{2+} release) of respiratory muscles under many different conditions (Brown et al., 1991; Doherty & Smith, 2005; Mazzarelli, Jaspar, Zin, Aranda, & Milicemili, 1986; Santalla, 2001; Supinski et al., 1986). A caffeine-induced improvement in respiratory muscle recruitment and contractility may help overcome some of the resistance to thoracic excursions and aid some of the increased inspiratory and expiratory muscle work that is associated with the SCBA regulator and harness.

Why caffeine ingestion increased $\dot{V}_E$ and V_t without changing RR, $\dot{V}O_2$, and $\dot{V}CO_2$ is less clear but may involve direct stimulation of medullary respiratory neurons and/or a thermal induced hyperpnea (increased $\dot{V}_E$ due to increased V_t at relatively low RR). Previous research that involved fixed work loads and had no changes in $\dot{V}O_2$ and/or increases in V_t with caffeine found a decrease in $\dot{V}_E$ (Brown et al., 1991; Santalla, 2001). These authors attributed decreases in $\dot{V}_E$ to increased alveolar ventilation (as suggested by a decrease in the ratio of physiological dead space to tidal volume) (Brown et al., 1991; Doherty & Smith, 2005). Further support is found from slower $\dot{V}_E$ kinetics with ingestion of caffeine and exercise at 50% and 80% $\dot{V}O_{2max}$ without altering $\dot{V}O_2$ kinetics (Bell, Kowalchuk, Paterson, Scheuermann, & Cunningham, 1999). These findings are contradictory to the data in the present study.

Caffeine has been implicated to elicit effects on several different respiratory control mechanisms. The first that might explain greater tidal volumes is a caffeine-induced bronchodilation (Durzo, A. D., Jhirad, R., Jenne, H., Avendano, M. A., Rubenstein, I., & Dcosta, M, 1990). Caffeine has also been observed to directly act on medullary respiratory neurons (Bell et al., 1999; Eldridge, Millhorn, Waldrop, & Kiley, 1983; Mazzarelli et al., 1986). However, when studying $\dot{V}_E$ in intact organisms the interaction between carotid body and vagal reflexes, changes in medullary extracellular pH, changes in whole body metabolism, and adrenal gland catecholamine release must be accounted for to determine respiratory control (Bairam, A., DeGrandpre, P., Dauphin, C., & Marchal, 1997; Bell et al., 1999; Durzo et al., 1990; Eldridge et al., 1983; Mazzarelli et al., 1986). In this current study, no differences in RER, $\dot{V}O_2$, and BLa imply pH and whole body metabolism was not different between CAFF and PLA.

The increased $\dot{V}_E$ with caffeine is more likely caused by modulations in carotid body and vagal reflexes and/or adrenal gland catecholamine release (Durzo et al., 1990). Carotid body reflexes that influence $\dot{V}_E$ sensitivity include P_aCO_2, pH, catecholamines, and temperature (Durzo et al., 1990). However, previous research has not identified caffeine-induced changes in P_aCO_2 and pH (Durzo et al., 1990). The elevated T_c (Figure 2) observed in the present study may have altered peripheral chemoreceptor activity and increased $\dot{V}_E$ (Durzo et al., 1990).

Thermal hyperpnea in an attempt to cool the upper airways of the body may be involved in the hyperventilation observed in the present study after caffeine ingestion. Respiratory heat loss in humans can lead to a 46% total loss of cephalic heat loss even during light exercise activity and relatively low $\dot{V}_E$ (White, 2006). It is possible that the differences in T_c between caffeine and placebo trials is the influential stimulus for the increased $\dot{V}_E$ and V_t observed with caffeine ingestion observed in this study.

Alternatively, it maybe a combination of direct caffeine stimulation of medullary respiratory neurons and increased temperature detected by the carotid body.

The changes in $\dot{V}_E$ with caffeine led to significant increases in total air consumed during the three work bouts (Figure 1). These data are of interest to firefighting as it relates to the amount of time a firefighter can work while breathing through an SCBA during emergency situations. The current SCBA tanks used by most Fire Departments are designed to elicit approximately 30- 45 min of air, which translates into 15-30 min of work time per bottle. The data from the current study suggest that the work time a firefighter would have per air bottle would be significantly less if an equivalent of 6 $mg \cdot kg^{-1}$ of caffeine was ingested before hand. Furthermore, if the emergency situation requires repeated work intervals, caffeine would inflate air consumption shortening the time a firefighter would be able to work even further on each subsequent SCBA bottle.

Core Temperature

The most novel observation of the present study is that a 6 $mg \cdot kg^{-1}$ of caffeine dose increased T_c during three 10 min work bouts at VT-1 wearing full firefighter PPE and breathing through an SCBA (Figure 2). To our knowledge this is the first exercise study in humans to detect a difference in any body temperature measure after ingestion of caffeine (Armstrong, 2002; Armstrong, Casa, Maresh, & Ganio, 2007; Cohen, 1996; Dunagan, 1998; McLean, 2002; Roti, 2006; Stebbins, 2001). There are very few studies that have monitored the effects of caffeine on exercise-heat tolerance in response to an environmental temperature stress; however, unlike the present study, the aforementioned research applied environmental heat stresses, had small samples sizes (therefore presumably low statistical power), and did not always use subjects as their own controls

(Armstrong et al., 2007). Therefore, the previous literature may not be comparable to the present study in which the heat stress was mostly metabolically derived to create a unique microclimate in the PPE.

The mechanism involved for the caffeine-induced hyperthermia observed in this study is unknown. However, in mice, introduction of adenosine agonists (both A_1 and A_2 sub units) invoked hypothermia and that methylxanthines (caffeine and theophylline) as an adenosine receptor antagonist have been shown to reverse or reduce this effect (Zarrindast & Heidari, 1993). The authors attribute the change in body temperature to a blockade of adenosine A_2 activated vasodilatation in the periphery (Zarrindast & Heidari, 1993).

In addition, a known side effect of caffeine ingestion during exercise is increased level of plasma epinephrine (Graham & Spriet, 1995; Jackman, Wendling, Friars, & Graham, 1996; Van Soeren, 1998). The exercise, heat, and dehydration stimulus during this current experiment could have induced an extreme epinephrine response. Large epinephrine responses have been theorized to superimpose a vasoconstriction on the active vasodialtory response needed for adequate thermoregulation (Coyle & Montain, 1992; Coyle, 1998; Coyle & Gonzalez, 2001; Gonzalez-Alonso, 1999; Wingo, 2005; MoraRodriguez, 1996). In fact, infusion of epinephrine while cycling at 65% $\dot{V}O_{2max}$ in 33°C heat resulted in diminished skin blood flow and increase in T_c compared to control (MoraRodriguez, 1996). Thus, plasma epinephrine has a role in adrenergic vasoconstriction of the skin, which causes hyperthermia during exercise (MoraRodriguez, 1996). In the current study, if caffeine inhibited peripheral vasodilatation in combination with a superimposed epinephrine adrenergic vasoconstriction, it could possibly explain the increases in T_c without a difference in sweat loss during the CAFF condition as shown by previous research (MoraRodriguez, 1996). However, catecholamines were not measured and the above hypothesis would need to be tested by further research.

Caffeine via adenosine A_{2a} receptor antagonism has also been implicated to increase dopaminergic and catecholaminergic transmission centrally (Kalmar & Cafarelli, 2004a; Kalmar & Cafarelli, 2004b; Kalmar, 2005). Recent data using dopamine/norepinephrine reuptake inhibitors (thus increasing transmission similarly to caffeine) found increased core temperature in endurance trained males during time trial cycling in both temperate (18 ^oC) and warm (30 ^oC) temperatures (Watson, Hasegawa, Roelands, Piacentini, Looverie, & Meeusen, 2005). These assumptions were made from increased extracellular dopamine and norepinephrine levels in the preoptic area and anterior hypothalamus (which is central to thermoregulation during exercise) observed in rats during similar exercise and environmental conditions to the same inhibitor (bupropion) (Hasegawa, Piacentini, Sarre, Michotte, Ishiwata, & Mecusen, 2008). Although this is purely speculative, if caffeine induced a dopamine/norepinephrine response similar to bupropion it could explain the increased T_c observed. However, more research is needed identify this possibility.

Another novel finding of this study is that caffeine increased calculated physiological strain index (PSI) throughout the exercise (Figure 3). The PSI difference caused by caffeine is mainly due to changes in T_c rather than HR. PSI followed a similar trend to T_c such that as work progressed the difference between caffeine and placebo widened (Figures 2 and 3). From these data it is apparent that without an observed difference in HR, the difference in physiological strain between conditions was the result of a greater thermal load under the CAFF condition. These data suggest that during three repeated work bouts in PPE and SCBA breathing a person may be more susceptible to heat illness or injury if a dose of 6 $mg \cdot kg^{-1}$ of caffeine or equivalent is ingested. Therefore, it may be in the interest of firefighters to curb their caffeine habits during work days. These data are also in accordance with previous research that caffeine does not apply any additional stress to the cardiovascular system by means of HR during exercise under heat stress (McLean, 2002; Roti, 2006).

Perceptual Variables

Caffeine was also able to reduce the average rating of perceived exertion (RPE) on the 10pt Borg scale during three 10 minute repeated work bouts at VT-1 (Table 4). This is not an uncommon observation. A meta-analysis analyzing the effects of single dose of caffeine (oral ingestion) on perceived exertion during whole body exercise revealed caffeine ingestion reduced RPE by approximately 6% during constant rate exercise (Doherty & Smith, 2005). The literature search identified 44 studies, in which 48% (21 studies) met the inclusion criteria set by the authors (laboratory-based, placebo controlled, double-blind, published in a peer-reviewed journal) (Doherty & Smith, 2005). The authors suggested that caffeine resulted in an improvement in ventilatory efficiency was the main cause of the reduction in RPE (Doherty & Smith, 2005). This is an unlikely explanation for the reduction in RPE in the present study due to the increase in $\dot{V}_E$ and V_t with no differences in $\dot{V}O_2$ and RR observed in the caffeine condition. It is more likely that caffeine altered the participant's sensation of force and pain. Caffeine is known to alter afferent feedback and alter force and pain sensations during skeletal muscle contractions (Kalmar, 2005). The mechanisms involved in caffeine's effect on pain transmission are complex and poorly understood. However, it is accepted that a caffeine adenosine receptor antagonism can alter pain transmission peripherally, spinally, and supraspinally (Sawynok, 1998; Fredholm et al., 1999; Kalmar, 2005). The ventilatory data of the current study does not support the hypothesis of a caffeine enhanced ventilatory efficiency, therefore, caffeine stimulated analgesic effect is more likely to alter the perception of effort observed.

Conversely, perceived thermal distress was not different between caffeine and placebo trials (Table 4). This observation may be of significance due to the fact that T_c was elevated during CAFF trials. It is unknown if the scale is sensitive enough to detect the changes in a subject's perception of temperature or if any of the above mechanisms would be involved in the perception of heat as well. The ability of caffeine to alter the perception of work may have both positive and negative effects on firefighter's work tolerance. It is likely to allow firefighters to work harder in extreme emergency situations that require them to do so. It would also likely cause firefighters to work under physiological dangerous conditions from which they should be given time to recover.

Metabolism

It is apparent that caffeine did not alter whole body metabolism as indicated by no differences in $\dot{V}O_2$, RER, and BLa between CAFF and PLA during the three 10 minute work bouts. There is a consistent report of increases in plasma glycerol and free fatty acids (FFA) with caffeine ingestion at both rest and during exercise (Battram, 2004; Greer, 1998; Mohr, 1998). However, the literature does not support a significant difference between caffeine and placebo in net fatty acid uptake by the leg at rest or exercise (Acheson, 2004; Graham, 2000). Additionally, Graham, (2000) reports no change in net glycerol release from muscle, as well as no indication of a decrease in respiratory exchange ratio (RER) nor increase in leg $\dot{V}O_2$. These data are in agreement with the findings of the present study.

Conversely, the lack of a difference in BLa between caffeine and placebo is not in agreement with the literature. Continuous cycling at 70% and 65% $\dot{V}O_{2max}$ for 1 hour yielded increases arterial lactate (Graham, 2000; Roy, 2001). Direct catheterization of the femoral artery and vein coupled with muscle biopsies during caffeine ingestion and exercise at 70% $\dot{V}O_{2max}$ did not show an increase in exercising leg lactate release or muscle lactate (Graham, 2000). These facts indicate that the increased arterial lactate concentration associated with caffeine ingestion is likely caused by inhibition of lactate clearance by the liver or resting muscle or an increased release from other non-working tissues and not increased metabolism (Graham, 2000). However, this phenomenon may be dependent on the intensity and duration of the exercise. The low levels of BLa detected in this study indicate the metabolic demand was mostly aerobic (Table 3). Furthermore, the differences may be in lactate measurement technique (arterial compared to capillarized).

Conclusion

In summary, a 6 $mg \cdot kg^{-1}$ dose of pure caffeine caused a difference in ventilatory, perceptual, and core temperature responses to three 10 minute work bouts. Caffeine increased $\dot{V}_E$ and V_t, while causing no changes in RR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, HR and oxyhemaglobin saturation. This is probably caused by a thermal hyperpnea activated by the carotid body reacting to the caffeine-induced elevation in T_c in combination with caffeine directly stimulating medullary respiratory neurons. The increased T_c observed in the caffeine trials induced a higher physiological strain. Increased T_c may be related to adenosine antagonism in peripheral blood vessels, an extreme epinephrine response, and/or supraspinal dopaminergic and catecholaminergic actions on the preoptic area and anterior hypothalamus. However, this is all speculative and further research is needed to support or refute the above physiological mechanisms. Caffeine also reduced RPE when compared to placebo. The RPE reduction is mostly likely explained by an analgesic effect of caffeine rather than caffeine enhanced ventilatory volume.

Practical Application

The results of this study suggest pure caffeine consumption should be monitored in firefighters. Caffeine increases the physiological strain in firefighters (due to increased T_c), causing them to consume more air while simultaneously dampening their perception of work. These results suggest that during repeated work bouts, caffeine will make firefighters more susceptible to heat illness or injury compared to placebo. Moreover, increased air consumption caused by caffeine would reduce the amount of time that a firefighter would be able to work while breathing through an SCBA especially in an emergency scenario that would require them to repeat work with limited or no rest. Additionally, caffeine altering the perception of work implies that firefighters may need to have their vital signs closely monitored to determine work to rest ratios. Because of their altered perception of work with caffeine-use firefighters may be less likely to report to rehabilitation sites themselves.

Future research should attempt to identify the mechanisms are involved in increased core temperatures caused by caffeine, the effect of coffee opposed to pure caffeine on core temperature, as well as, examine the possibility of a dose response relationship to during firefighter related work.

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Appendix A – Review of Literature

Introduction

Caffeine is the most common and widely used drug in the world. It is consumed mostly in forms of coffee and tea, as well as, many other products such as chocolate, soft drinks, and energy drinks (Fredholm et al., 1999). In North American the average coffee consumption is estimated at 2-4 cups of coffee each day, therefore, caffeine ingestion is approximately 200-400mg/day of caffeine (20-30% consume 600mg per day) (Armstrong, 2002).

The ingestion of caffeine has been associated with a variety of different affects on the body one of which is the ability to enhance exercise performance (Armstrong, 2002; Doherty, 2004b; Doherty & Smith, 2005; Graham & Spriet, 1995; Graham, 2001; Kalmar, 1999). Caffeine is considered an ergogenic aid by most research scientists and a variety of governing sports organizations, which have implemented highly regulated levels or complete have completely, barred it from the sport (Graham, 2001). Caffeine is considered a potent ergogenic aid because it is rapidly absorbed from the Gastro-Intestinal tract, plasma concentration is elevated in humans ~ 45min after ingestion and is maintained even during exhaustive exercise, and interacts with intended target tissues (has brain-to-plasma ratio of 80% and cerebrospinal fluid/plasma ratio of 52 %) (Fredholm et al., 1999; Graham & Spriet, 1995; Soto et al., 1994).

Ergogenic actions of caffeine have been hypothesized to enhance exercise performance by modulating cardiovascular, metabolic, and neurological variables without negatively affecting fluid balance or core temperature (Armstrong, 2002; Armstrong et al., 2005; Doherty, 2004b; Doherty & Smith, 2005; Graham, 2001; Maughan, 2003; Stebbins, 2001). Most research involving caffeine and exercise in heat stress apply environmental heat and humidity during exercise modalities of running or cycling in normal exercise attire of shorts and t-shirt which may not relate to the stress of exercise while wearing firefighter personal protective equipment (PPE). However, the micro-climate created by firefighter PPE and the resistance to breathing caused by a self-contained breathing apparatus (SCBA) are unique stresses in which the effect of caffeine on work tolerance is unknown. The micro-climate of firefighter PPE applies a distinctive heat stress by impeding the exchange of metabolic heat from the body into the atmosphere, thus increasing the risk of heat illness and injury when compared to most other occupations (Baker, 2000; Smith, 2001).

Anecdotal evidence suggests that caffeine ingestion (mostly in the forms of coffee and tea consumption) is abundant amongst firefighters and yet, there is no data on whether this behaviour should be monitored, controlled, or encouraged. .

The aim of this paper will be to identify the many effects of caffeine on the human body and any confounding variables that may alter the effects of caffeine on physiological variables during exercise. This paper will also analyze the data that implicate alteration of cardiovascular, metabolic, and neurological variables during exercise and the possible mechanisms that underlie the exercise performance improvements observed. This literature review will also attempt to compare the challenges of working in firefighter Personal protective equipment (PPE) while breathing through an SCBA to indicate if caffeine could possibly affect work tolerance under those unique exercise conditions. Various laboratory research based studies have identified numerous exercise variables to be altered by caffeine ingestion. They include; Heart rate, blood pressure, skeletal muscle metabolism, excitation-contraction coupling of skeletal muscle, the perception of fatigue or exertion, the perception of pain during exercise, and motor unit recruitment.

The Effects of Caffeine and Confounding Factors

Chemical Structure & Forms of Caffeine

Caffeine is a trimethylxanthine (1, 3, 7 trimethylxanthine in coffee, tea, and soft drinks) which is catabolised by the cytochrome P450 system in the liver to dimethylxanthines (Armstrong, 2002; Graham, 2001). The liver de-methylates caffeine to create 1 of 3 dimethylxanthines: paraxanthine, theophylline and theobromine which are released into the blood stream to interact with other tissues (Graham, 2001). It is the dimethylxanthines that act as an adenosine receptor antagonist, alter Ca^{2+} release in muscle cells, and affect cyclic adenosine monophosphate (cAMP) metabolism. Caffeine is abundant in many common foods in the western diet, coffee, tea, chocolate, and soft drinks are rich in caffeine, however, caffeine ingested in these forms have not been shown to be as a potent ergogenic aid as pure caffeine (Fredholm et al., 1999; Graham, 2001). The fact that the above sources have many other compounds that may be pharmacologically active is often overlooked. The interaction of the other compounds and caffeine within these sources, and the consequently affects on metabolism and ergogenic performance are unknown, yet are likely to be the reasons for the differences in performance (Graham, 2001).

Coffee vs. Caffeine

As stated above the ergogenic effects of coffee are inferior to those elicited by pure caffeine. Caffeine has improved time to exhaustion during a treadmill run at a pace similar to the subjects best 10km time while Ingestion of regular coffee had no effect (Graham, 2001). The authors concluded that the difference in performance could not be attributed to differences in caffeine absorption due to peak plasma caffeine concentrations and the actual caffeine concentrations were identical for both the caffeine and regular coffee groups (Graham, 2001).

Other studies that have compared regular coffee decaffeinated coffee and pure caffeine based on their ergogenic properties. A review conducted by Dr. Terry Graham from the University of Guelph found that pure caffeine inducing a greater exercise enhancement to coffee or decaffeinated coffee (Graham, 2001).

Graham et al, found a greater ergogenic effect with pure caffeine even when compared to regular coffee and decaffeinated coffee supplemented with pure caffeine. All trials delivered the same 4.45mg/kg dose, yet, pure caffeine increased exercise endurance drastically when compared to all other conditions. The authors attributed this difference to the fact that coffee has hundreds to thousands of compounds that are pharmacologically active; therefore, some of them may offset the effects of caffeine during exercise (Graham, 2001). More research is needed in this area to identify which compounds in coffee impair the magnitude of caffeine induced exercise enhancement and the mechanisms involved.

Fluid Balance

Generally speaking, there is a belief that caffeine has a negative effect on fluid balance especially during exercise. Conversely, there is no solid evidence in the scientific literature to support the assumption that caffeine increases dehydration during exercise (Armstrong, 2002). One particular study involving 480 ml of liquid containing caffeine (150 and 300mg) displayed equivocal evidence. While resting 3h Urine volume decreased 8% during 150mg condition and increased 17% during the 300mg condition (Armstrong, 2002). The assumption that caffeine ingestion prior or during exercise, particularly in the heat, may cause harmful dehydration or hyperthermia is based on 2 observations: Resting metabolic rate is increased by caffeine ingestion in both physically trained and sedentary subjects; this might add to heat production and result in hyperthermia (Armstrong, 2002). However, there have been no reports of significant differences in core body temperature, sweat loss, urine volume, and plasma volume (Armstrong, 2002). For further review on this topic please see the review article by Dr. Lawrence Armstrong in the reference section of this paper.

Tolerance of Caffeine

Caffeine is a drug that frequent ingestion of it will cause tissue adaptations (Graham, 2001). Tolerance can be developed in adults within 4-5 days (Armstrong, 2002). Use of animal models has shown adaptations (up-regulation of adenosine receptor numbers or alterations in receptor actions) in some tissues while other tissues do not adapt at all (Graham, 2001). Tolerance then usually requires a greater amount of caffeine to be consumed to induce the same physiological response viewed in non-users at rest

(Armstrong, 2002; Graham, 2001). Development of tolerance has responses of plasma epinephrine decreases, changes in respiratory variables and plasma FFA during rest; however, these values are not different from the effects of caffeine on non users during an incremental exercise test (Armstrong, 2002; Dodd, Brooks, Powers, & Tulley, 1991; Graham, 2001). Therefore, tolerance to caffeine does not seem to alter the ergogenic effects of caffeine and this limited information suggests that caffeine non-users and users respond similarly. Therefore, withdrawal from caffeine may not be important on the effects of exercise (Armstrong, 2002; Graham, 2001; Hetzler, Warhaftigglynn, Thompson, Dowling, & Weltman, 1994). Similarly, caffeine habituation has not been shown to relate to the response of caffeine on runners during a 1500m performance nor, caffeine induced changes in muscle force development (Hetzler et al., 1994). Time of withdrawal also does not seem to affect the ergogenic caffeine response during exercise. Withdrawal 0, 2, 12, 24, 48 hrs before steady state exercise and a 5mg/kg dose of caffeine did not alter any metabolic responses (endurance not measured) (Hetzler et al., 1994).

Timing & Dose

After ingestion of caffeine, one hour of rest is most common before starting any exercise trial. This is due to the fact that maximal caffeine absorption and plasma levels are seen in approximately 1hr after ingestion (Graham & Spriet, 1995).

The absorption of caffeine is unaffected by exercise or dehydration and is unlikely to be affected by body composition because caffeine is both H_2O and lipid soluble (Graham, 2001; McLean, 2002). The pharmokinetics of caffeine have been tested in both men and women during exercise in the heat and have found that caffeine doses indexed to body mass results in a consistent plasma caffeine concentration in both men and women

(Graham, 2001; McLean, 2002). Doses of 3-9 mg/kg have been shown to be the most effective at increasing endurance exercise performance (Doherty, 2004b; Graham, 2001). Doses above 9mg/kg can cause a "caffeine intoxication" making subjects mentally confused, unable to concentrate, talkative, giddy, and unable to perform simple tasks (Graham, 2001; Kerrigan & Lindsey, 2005). 6 and 9 mg/kg have been shown to be equally effective in increasing power during 2000m rowing performance, in opposition, 3 and 6 mg/kg has been shown to have a greater ergogenic effect than 9mg/kg during treadmill running to exhaustion at 85% $\dot{V}$ O_{2max} (Graham & Spriet, 1995; Graham, 2001). Because 9mg/kg can cause caffeine intoxication, 3-6mg/kg appears to be the optimal dose for obtaining an ergogenic result (Graham, 2001).

Effects of Caffeine on the Cardiovascular System

There is a common perception that caffeine alters heart rate (HR) and blood pressure (BP) and those alterations in these cardiovascular variables may be involved in the ergogenic actions of caffeine (Armstrong, 2002; Farag, 2005; Fredholm et al., 1999). Caffeine has been demonstrated to alter heart rate and $\dot{V}$ O_2, however, only at rest and only in caffeine naive subjects (Dodd et al., 1991; Graham, 2001). Conversely, during exercise the affect of caffeine on heart rate is vague but an increase in blood pressure has been observed in both caffeine naive and habituated subjects (Daniels, Mole, Shaffrath, & Stebbins, 1998; Dodd et al., 1991; Graham, 2000; Graham, 2001; Sondermeijer, 2002). Karatzis (2005), has demonstrated that caffeine (coffee) consumption in healthy young adults leads to an acute (1) increase in central systolic pressure without affecting significantly peripheral systolic pressure (2) increase in wave reflections accompanied by a possible increase of arterial stiffness at rest (Karatzis, 2005). The amount of coffee used in that particular study delivered an 80mg dose of caffeine which is a much smaller dose than most other studies that give 3-6 mg/kg dose which is approximately 2-3 cups of coffee (Karatzis, 2005; Stebbins, 2001). During cycling at 70% $\dot{V}O_{2max}$ blood pressure monitored through a direct arterial catheter and connection to Statham blood pressure transducer confirms a significant increase in blood pressure with no difference in HR with a 6mg/kg dose (Graham, 2000). It is hypothesized that increase in blood pressure may be a result of smooth muscle A_1 adenosine receptor inhibition caused by caffeine. An A_1 receptor inhibition would reduce the vasodilatation effects of adenosine, therefore, increasing blood pressure (Graham, 2000).

During exercise, HR seems to only be significantly different from placebo when coupled with heat stress (Hunter, 2002; Stebbins, 2001). However, both chronic and acute caffeine use during 90 min of walking and cycling has shown not increases in HR when compared to placebo (McLean, 2002; Roti, 2006). While 100km cycling time trial at 27^{o}C and cycling at 50% $\dot{V}O_{2max}$ for 35 min at 37^{o}C found caffeine to significantly increase HR. The authors of the these two studies do not offer any insight into the mechanism that may be involved with elevated HR with caffeine and heat but imply that elevated lactate as an indicator of increased muscle metabolites may explain the increase in HR (Stebbins, 2001). However, increased blood lactate with caffeine ingestion is not an uncommon observation in thermal neutral exercise experiments that have not observed increased heart rates; Thus, increased muscle metabolite production is an unlikely explanation (Graham, 2000; Graham, 2001). Authors who have observed increased HR with caffeine ingestion and exercise in heat do not measure nor attribute the increased HR to an increase sympathetic activity even though caffeine and heat are both known to stimulate the sympathetic nervous system (Graham & Spriet, 1995; Graham, 2001; Jackman et al., 1996; MoraRodriguez, 1996; Sondermeijer, 2002). Due to the fact that sympathetic nervous system is known to stimulate heart rate, it is not unreasonable to speculate that any increase in HR may be attributed to a greater sympathetic response caused by combined caffeine and heat stimulus rather than an increase in muscle metabolite production or adenosine receptor antagonism (Astrand et al., 2003).

The effects of caffeine on the cardiovascular system during exercise are unclear. HR does not seem to be affected when caffeine and exercise are coupled in thermal neutral environments (Dodd et al., 1991; Graham, 2000; Graham, 2001; Sondermeijer, 2002). In addition, there is contradictory evidence on the effect of caffeine and heat stress on exercising heart rates (Hunter, 2002; McLean, 2002; Roti, 2006; Stebbins, 2001). These data questions the validity of elevated exercising heart rate observations in both thermal neutral and heat stressed environments. More research would need to be conducted that focused specifically on caffeine's affect on exercising heart rates in heat to determine both the authenticity of an elevated heart rate and the role of heart rate on caffeine's overall ergogenic effect.

Caffeine does appear to enhance blood pressure in both resting and exercising conditions (Anderson, 2001; Karatzis, 2005). The increased BP is likely due to A_1 adenosine receptor antagonism of smooth muscle nullifying vasodilatory properties of adenosine (Graham, 2000). Again, the augmentation of BP by caffeine ingestion function in the overall ergogenic effect appears to be minimal. The literature implies that caffeine induced enhanced blood pressure may aided exercise enhancement but is not solely responsible.

Effects of Caffeine on Skeletal Muscle Metabolism

Carbohydrate (CHO) & Fat Metabolism

Historically, caffeine has been hypothesized to elicit an ergogenic effect by altering CHO /Fat metabolism ratio to produce a glycogen sparing effect (Graham, 2001). However, recent data contests the reality of a caffeine induced glycogen sparing effect (Jackman et al., 1996).

The major observation that is offered in support of a caffeine glycogen sparing effect is the consistent report of increases in plasma glycerol and free fatty acids (FFA) with caffeine ingestion at rest and during exercise (Battram, 2004; Greer, 1998; Mohr, 1998). The enhancement arterial FFA and glycerol suggests that caffeine increases lipolysis in adipose tissue and that theses increases are likely caused either by increased catecholamines or direct adenosine antagonism. However, evidence does not support there to be a significant difference between caffeine and placebo in net fatty acid uptake by the leg at rest or exercise (Acheson, 2004; Graham, 2000). Additionally, there is data that reports no change in net glycerol release from muscle, as well as, no indication of a decrease in respiratory exchange ratio (RER) nor increase in leg $\dot{V}\,O_2$ (Graham, 2000). Further evidence refuting the existence of a caffeine induced glycogen sparing effect can be drawn from a study that found lower levels of caffeine ingestion (3mg/kg & 6mg/kg) elicited a greater time to exhaustion (treadmill running at 85% $\dot{V}\,O_{2max}$) without the accompanying increasing with FFA and epinephrine increases that were observed with a

9mg/kg dose (Graham & Spriet, 1995). Based on these data, it is unlikely that any alteration in CHO and/or fat metabolism that may be caused by ingestion of caffeine is a vital component to the exercise enhancement that is steadily observed. (Graham, 2000; Roy, 2001).

Lactate

Caffeine has also been shown to increase plasma lactate concentrations during exercise (Graham, 2000; Roy, 2001; Stebbins, 2001). However, this phenomenon may be dependent on the intensity of the exercise. During cycling exercise at $\dot{V}O_{2max}$, muscle lactate not blood lactate has been reported to be different between placebo and caffeine trials involving exercise durations of 2 minutes and until exhaustion (Jackman et al., 1996). Conversely, continuous cycling at 70% and 65% $\dot{V}O_{2max}$ for 1 hour duration yielded increases arterial lactate (Graham, 2000; Roy, 2001). The increased plasma lactate indicates an increase in lactate production/release in the muscle and/or a decrease in lactate clearance from circulation by the liver and non exercising muscle (Roy, 2001). Direct catheterization of the femoral artery and vein coupled with muscle biopsies during caffeine ingestion and exercise at 70% $\dot{V}O_{2max}$ did not observe an increase in exercising leg lactate release or muscle lactate (Graham, 2000). These facts indicate that the increased arterial lactate concentration associated with caffeine ingestion is likely caused by inhibition of lactate clearance by liver or resting muscle or an increased release from other non working tissues (Graham, 2000). In terms of caffeine's ergogenic properties, increased blood and muscle lactate concentrations have not led to performance decrement. This information indicates that the H+ ion associated with lactate is excreted and buffered from working muscle and blood. However, there is no data on the effects of caffeine ingestion and exercise on blood or muscle pH to support or refute this hypothesis.

From the literature it is apparent that caffeine does have an effect on exercise metabolism (Graham & Spriet, 1995; Graham, 2001; Jackman et al., 1996). The evidence however seems to suggest that caffeine's ergogenic effect does not result predominantly from metabolic actions (Acheson, 2004; Graham, 2000; Greer, 1998; Jackman et al., 1996).

The Effects of Caffeine on Excitation-Contraction Coupling of Skeletal Muscle

Caffeine has been proven to enhance the excitation-contraction coupling of skeletal muscle ((Graham, 2001; R. James, 2005). However, the relevance of caffeine's direct action on skeletal muscle as a mechanism for human work performance is highly debatable.

Calcium release

The excitation–contraction coupling of skeletal muscle is stimulated by an action potential traveling along the sarcolemma and into the T-Tubule (transverse tubule) system. The voltage change is detected by Dihydropyridine receptor (DHPR) which in turn, removes Mg^{2+}/FK506 binding protein inhibition of Ca^{2+} release from ryanodine receptors (RyR) of the sarcoplasmic reticulum (SR). Additionally, intracellular Ca^{2+} binds to an activation site on the RyR stimulating Ca^{2+} release (Lamb, 1999). In vitro experiments have proven caffeine will cause muscle contraction in the absence of membrane depolarization, increase titanic force, and decrease rate of relaxation (Kalmar, 2005). These phenomena are credited to increased release of Ca^{2+} from the SR via interaction with ryanodine receptors. It has been proposed that caffeine increases muscle force by direct action of Ca^{2+}, activated Ca^{2+}channels of the RyR of the SR (Fredholm et al., 1999; Graham, 2001; R. James, 2005). This fact is further supported by observations in mouse muscle in which muscles that produced more force in response to caffeine, also had larger amounts of RyR3 ryanodine receptor type (R. James, 2005). It appears that the sensitivity of RyRs active site for Ca^{2+} in the presence of caffeine is increased, such that, lower Ca^{2+} concentrations can become stimulatory. Enhanced contractility caused by local actions of caffeine on the muscle involved in the excitation-contraction coupling (Ca^{2+} release via RyR) would translate to at least part of the increased work performance that is caused by caffeine ingestion (Graham, 2001). However, Ca^{2+} release from RyR has only been directly observed under caffeine concentrations of 70μM, which is considered toxic to humans ((Kalmar, 2005). Most caffeine research on human subjects consists of a single oral dose of 6mg/kg eliciting approximately 40μM plasma caffeine concentration (Graham & Spriet, 1995).

There is recent evidence supporting the lack of significant caffeine-induced Ca^{2+} release from a 6mg/kg dose (~40μM plasma caffeine concentration). A study published in 2006 by Kalmar & Cafarelli where subjects completed measures of knee extension torque before and after ingestion of caffeine or placebo. Measures of maximal voluntary activation, peripheral transmission, contractile properties and central excitability were taken. A supramaximal pulse was administered (via the femoral nerve) during and immediately after a maximum voluntary contraction (MVC) to quantify % voluntary activation using the twitch interpolation technique and to assess maximal action potential

(M-wave) and contractile properties. Caffeine had no effect on M-wave amplitude, peak twitch tension, or maximal instantaneous rate of twitch relaxation. The authors claim the plasma caffeine levels were too low to increase the development of muscle tension (Kalmar & Cafarelli, 2006). These data coincide with a review written by the same group which they state caffeine has no effect of on twitch amplitude, twitch ½ relaxation time, or maximal instantaneous rate of twitch relaxation in either fatigued or non-fatigued muscle in most humans studies (Kalmar, 2005).

In contrast, there are human studies that report delayed failure and enhanced recovery of contractile properties after fatiguing electrical stimulation, therefore, the possibility that caffeine may directly affect skeletal muscle in some instances cannot be discounted (Graham, 2001; Kalmar & Cafarelli, 2004a; Mohr, 1998). For example, caffeine has been reported to increase diaphragm contractility by 48%, increase tension of adductor pollicis at submaximal stimulation levels, increase MVC by 3.5%, and improve time to fatigue at 50% of MVC by 26%, all at plasma caffeine levels less than 70μM (Graham, 2001). The most convincing argument for caffeine having a direct affect on skeletal muscle was made from Mohr et al., 1998 and their study of caffeine ingestion in tetraplegics and paraplegics. In this experiment, the participants paralyzed legs were electrically stimulated to perform cycling at a constant resistance until fatigue (defined as < 35 rev/min) after either 6mg/kg caffeine ingestion or placebo. $\dot{V}\,O_2$, respiratory exchange ratio, and plasma epinephrine were not different in either condition; however, caffeine increased time to exhaustion by 6%. Without influence from the brain or alterations in metabolism, caffeine-enhanced muscle function via increased Ca^{2+} release could account for the increased endurance (Mohr, 1998). The authors also speculated that metabolic changes that have been observed in vitro such as previous stimulation of the RyR, an increase in palmitoyl-CoA, or an increase in cADP-ribose (metabolite of NAD) can dramatically increase the sensitivity of calcium mechanisms to caffeine, therefore, increase force generation per motor unit and time to fatigue (Mohr, 1998).

The conflicting data concerning caffeine's involvement in Ca^{2+} release as a contributing factor in the ergogenic properties may be related to the type of muscular contraction. It seems that generally, caffeine increased force development during submaximal and dynamic contractions, while maximal isometric contractions yield little or no effect.

Ion Balance

Caffeine has also been shown to alter another aspect of excitation contraction coupling, ion balance. Na^+ and K^+ balance is important during exercise to maintain muscle membrane potential and excitability, therefore, alteration in Na^+ and K^+ fluxes across the sarcolemma would affect muscle performance (McKenna, 1999). During exercise there is an obvious increase rate of membrane depolarization. Subsequent increases in Na^+ influx and K^+ efflux causes an irregular concentration of intracellular Na^+ and extracellular K^+. This alteration in ion balance has been calculated to cause a 13mV decrease in membrane potential during fatiguing knee extensor exercise in humans (McKenna, 1999). Decreases in membrane potential may be involved in muscle fatigue. It is hypothesized that K^+ shifts cause t-tubular depolarization and inactivation of fast Na^+ channels, consequently diminishing action potential development and transmission. As a result this would reduce DHPR activation, hence, lowering Ca^{2+} release from the SR, therefore, less force generation from the motor unit (McKenna, 1999). Caffeine ingestion has resulted in reduced levels of plasma K^+ during exercise (Graham, 2001). It appears that there must be less release of K^+ from active muscle or faster plasma clearance. This may be caused by caffeine and/or the associated caffeine increase in epinephrine stimulation of resting muscle Na^+/K^+ ATPase to take up more potassium (Graham, 2001). In response to exercise caffeine ingestion participants had less of an increase in arterial K^+ but K^+ release from active leg was unaltered. Therefore, the effects of caffeine or elevated epinephrine could not be determined (Graham, 2000). Caffeine has only been directly shown to stimulate muscle K^+ uptake in resting muscle and only in non-physiological concentrations of plasma caffeine (Lindinger et al., 1996). However, the greatest evidence for caffeine acting as a direct signal for K^+ uptake was observed in tetraplegics who had less of an increase in circulating K^+ coupled with unaltered epinephrine levels (Graham, 2001). Hence, caffeine is stimulated K^+ uptake aids the maintenance of membrane potential and resultant action potential transmission which would likely delay fatigue.

It is clear that caffeine can alter the excitation-contraction coupling properties of skeletal muscle, however, most of the research that detect improvement in muscle performance are in vitro studies conducted under non-physiological plasma caffeine levels (≥70μM) (R. James, 2005; Kalmar, 2005). In opposition, there is enough in vivo evidence to speculate that physiological plasma caffeine levels (40-45 μM) can have an effect on the excitation-contraction coupling by altering Ca^{2+} release (increasing force of contraction) and ion balance (maintaining membrane potential), just not to the magnitude that has been observed in vitro (Graham, 2001; Mohr, 1998). Therefore, it is probable a portion of caffeine’s ergogenic effect is due to enhancement of excitation-contraction coupling.

Effects of Caffeine Ingestion on the Perception of Work

Caffeine has also been hypothesized to alter human’s perception of work. The lowering of participants rating of perceived exertion (RPE) during exercise may be apart of the mechanism involved with increases in endurance and power output during exercise that have been observed after caffeine ingestion.

A meta-analysis was published in 2005 analyzing the effects of single dose of caffeine (oral ingestion) on perceived exertion during whole body exercise. The literature search identified 44 studies, in which 48% (21 studies) met the inclusion criteria set by the authors (laboratory-based, placebo controlled, double-blind, published in a peer-reviewed journal) (Doherty & Smith, 2005). This search yielded an analysis of 202 participants and calculated 109 RPE effect sizes (Effect size = mean caffeine- mean placebo/ standard deviation of placebo).

Examination of the data revealed caffeine ingestion reduced RPE by approximately 6% during constant rate exercise and improved performance of 11% (Doherty & Smith, 2005). The lowered RPE reported during exercise obviously indicates that caffeine must downgrade the perceptual response of exercise. Therefore, the authors presume that participants in the reviewed studies must have had a greater capacity to tolerate the discomfort associated with fatigue during exercise, thus, caffeine altered the perception of fatigue (Doherty & Smith, 2005). This conclusion would only explain the ergogenic effects of caffeine in studies where the participants worked to volitional exhaustion (Doherty & Smith, 2005). However, the meta-analysis also revealed that participants in studies without a fixed worked rate chose a higher intensity of exercise when caffeine trials are compared to placebo. In which case, the above hypothesis does not apply. Thus, caffeine's alteration of perceptual response must allow subjects to centrally recruit and engage more motor units, allowing for increased power output during time-trial based exercise tests (Doherty & Smith, 2005). Although there is no direct evidence, caffeine does affect both the motor and sensory pathways which could independently or in combination alter RPE during exercise (Doherty, 2004a; Doherty & Smith, 2005; Fredholm et al., 1999; Kalmar & Cafarelli, 2004b; Kalmar, 2005; Walton, Kalmar, & Cafarelli, 2003). Furthermore, Doherty et al., implicate caffeine's ability to alter the work of breathing to explain reduced RPE values. Metabolic cost ($V0_2$) of works has been suggested to be the most important determinant of RPE (Noble & Robertson, 1996). Caffeine is a known respiratory stimulant that augments ventilation under exercise conditions (Doherty & Smith, 2005). Ingestion of caffeine has been shown to significantly reduce the slow component of $\dot{V}O_2$ in well-trained runners exercising at 90% $\dot{V}O_{2max}$ which corresponded to a reduction in ventilation (Santalla, 2001). Additional evidence supporting caffeine's effect on respiration during exercise is provided by Doherty et al., by noting caffeine ingestion causes more efficient ventilatory volume, increased alveolar ventilation and a decrease in the ratio of physiological dead space to tidal volume during work at 50% $\dot{V}O_{2max}$ (Doherty & Smith, 2005). A more efficient respiratory system may facilitate an enhanced blood flow to the working muscle which could explain both the enhancement of performance and reduction of RPE observed with caffeine ingestion.

Two other interesting findings of the meta-analysis is that moderator variables including period of withdrawal from caffeine prior to treatment (range of 12-168hrs, median of 24hrs), interval between caffeine ingestion and exercise (range 30-360 min, median 60min), and administered caffeine dose (range 4-10mg/kg, median 6mg/kg), did not appear to have any major effects on RPE (Doherty & Smith, 2005). The second finding is that participants with the highest $\dot{V}\,O_{2max}$ values tended to have the largest reduction in RPE during exercise after caffeine ingestion (Doherty & Smith, 2005). The authors justified their findings with support from previous studies that found trained athletes to be more responsive to caffeine in terms of increased metabolic rate, increased epinephrine in the blood, and larger magnitude of time trial performance increases when compared to non-athletes (Doherty & Smith, 2005). Finally, Doherty and Smith cite a study that observed increases the density and sensitivity of adenosine A_1 receptors in swine with exercise training. Therefore, trained individuals have tissues that may be more responsive to the caffeine stimulus (Doherty & Smith, 2005). Conversely, if a tissue had greater density and sensitivity of adenosine A_1 receptors, there would be more active sites in which adenosine would have the opportunity to bind and apply inhibitory actions. Therefore, the influence of exercise training and adenosine A_1 receptor adaptation must be further researched.

Therefore, caffeine decreases RPE through a number of mechanisms. It is most likely that a reduction of RPE is related to the effort of breathing, and alterations in motor and sensory pathways. Moreover, withdrawal from caffeine, timing between ingestion and exercise, and magnitude of dosage do not appear to affect RPE during laboratory studies. Also, individuals with greater training status appear to be more affected by caffeine than non-trained individuals with respect to RPE values. Caffeine's ability to lower RPE is certainly complex and related to the ergogenic effects. However an area that is not discussed in great detail is the ability of caffeine to alter analgesia that may also be a key mechanism in the reduction of RPE during exercise and subsequent improved performance.

The Effects of Caffeine on Afferent Feedback: Pain and Force Sensation

The ergogenic effects of caffeine have also been implicated to caffeine-induced analgesia (analgesia is the absence of the sense of pain without loss of consciousness), especially with reference to increased endurance time. The capability of caffeine to antagonize adenosine receptors (will be discussed in detail in motor recruitment) is believed to be the mechanism of analgesia.

The inherent difficulty in assessing pain and comparing studies that evaluate pain is that pain itself and scales use to assess pain are completely subjective (Kalmar, 2005). Nonetheless, there are three studies that have examined the effect of caffeine on muscle pain and sensation of force. Motl et al., 2003 administered a 10 mg/kg dose to participants that cycled at 60% $\dot{V}\,O_{2max}$ for 30min to examine the effects of caffeine on muscle contraction pain. Participants ranked pain using a 10pt numerical every 5 min during the exercise bout. By the end of the exercise bout pain was ranked significantly lower in the caffeine trial compared to that of the placebo trial (Kalmar, 2005; Motl et al., 2003). In the second study, researchers occluded blood flow to forearm during a 1 min set of wrist curls to produce ischemia and muscle pain. A visual analog scale was used to assess pain in 15s intervals. Compared to placebo trial, 200mg dose of caffeine decreased pain at 15 and 30s but no at the end of exercise (Kalmar, 2005). In the third study, the purpose was to try and assess a constant sensation contraction to provide a more objective quantification of force sensations during sustained, submaximal, isometric knee extension (Kalmar, 2005; Plaskett & Cafarelli, 2001). Subjects were asked to reach a target force of 50% of their maximal voluntary torque. Once the target force was met the visual feedback was removed, and the subject was asked to maintain a contraction with the same "sensation" of force for 100s (Plaskett & Cafarelli, 2001). The researchers state that force does not degrade in a linear fashion, thus, the use of the double-exponential function, $Y = C + Ae^{-K1t\,+}\,Be\text{-}^{K2t}$ where Y is force, *t* is time, A and B are the values of the exponential process, C is the asymptote, and K1 and K2 are the rate constants (Plaskett & Cafarelli, 2001). The results showed that the first rate constant (K1) was significantly slower in the caffeine trial, while the second rate constant (K2) was not different between trials (Figure 3) (Plaskett & Cafarelli, 2001). Also, the force at the end of the 100s contraction was no different between trials (11.5+/- 2.2% MVC Placebo, 10.3 +/- 1.4% MVC caffeine) (Plaskett & Cafarelli, 2001). The authors concluded that subjects must decrease torque as the contraction progresses and discomfort increases in order to maintain the "same sensation" of a constant torque (Kalmar, 2005; Plaskett & Cafarelli, 2001). Moreover, due to the slower force decay rate in the caffeine trial, the authors presume a reduction in force sensation in the first 10-20s of the contraction must have also taken place (Kalmar, 2005; Plaskett & Cafarelli, 2001). However, there is no report of the % MVC values being significantly different between the two conditions during the 10-20s time intervals. Because the % MVC values were not different at the end-point of the 100s contractions and the 2nd rate of force decay (K2) was not different, without knowing if a difference in force exists with in the first 20s it is difficult to conclude that caffeine had any functional ergogenic effect during this protocol. Nevertheless, caffeine is likely to have an effect on nociception (the perception of pain or injurious stimuli) because adenosine has many roles that occur in multiple sites in the peripheral nervous system and CNS (Kalmar, 2005). Inhibitors of adenosine can produce both anti-nociceptive and anti-inflammatory properties which are mediated by different adenosine receptor populations (A_1, A_2) and are due to independent actions (Sawynok, 1998). Conversely, adenosine can have pro or anti-nociceptive depending on the location and receptor sub-type it interacts with (Kalmar, 2005; Sawynok, 1998).

Adenosine receptors and peripheral pain reception

Caffeine may prevent pain transmission actions of adenosine at peripheral nerve terminals (Sawynok, 1998). However, the local administration of caffeine has not demonstrated any anti-nociceptive properties most likely due to of its non-specific blockade of A_1 and A_2 receptors. Actions of A_1 receptor agonists locally in the hind paw of a rat inhibited pain transmission. A_1 receptor agonists must act directly on the sensory nerve terminal itself resulting in the inhibition of adenylate cyclase and decreased production of cyclic adenosine 3', 5' monophosphate (cAMP) (Sawynok, 1998). A_1 receptors are present on the cell body of dorsal root ganglion cells and on the central terminals of primary afferent neurons (Sawynok, 1998). Adenosine can also inhibit the release of excitatory amino acids; this action results from inhibition of Ca^{2+} entry into nerve terminals (Sawynok, 1998). Therefore the binding of adenosine to an A_1 receptor is likely to impede pain transmission in the periphery. In opposition, administration of an A_2 agonist in the periphery enhanced pain response due to A_2 receptor activation of adenylate cyclase resulting in an increase in cAMP levels within the sensory nerve terminals (Sawynok, 1998).

Spinal and Supraspinal

Less is known about the spinal and supraspinal effects of caffeine on nociception. Serotonergic action at the spinal level has been implicated in anti-nociception (Kalmar & Cafarelli, 2004a). At the spinal level, adenosine receptors are localized primarily on neurons post-synaptic to primary afferents and descending projections within the dorsal horn but some receptors are present on central terminals of primary afferent neurons (Sawynok, 1998). Caffeine is known to enter cerebrospinal fluid and therefore is likely to act A_1 and A_2 which are equal in number in the spinal cord (Sawynok, 1998; Soto et al., 1994). Supraspinally caffeine would diminish pain via increased cholinergic, noradrenergic and serotonergic transmission (Fredholm et al., 1999; Kalmar, 2005). Yet, in contrast supraspinal administration of adenosine agonist has been found to be anti-nociceptive (Sawynok, 1998). The difference is likely that caffeine would obstruct presynaptic adenosine receptors on cholinergic nerve terminals while adenosine analogs act postsynaptically at other sites to produce anti-nociception (Sawynok, 1998).

The mechanisms involved in caffeine's effect on pain transmission are complex and poorly understood. Antagonism of adenosine receptors would be involved in analgesic properties of caffeine; however, blockade of A_1 receptors in the periphery would increase pain transmission while A_2 antagonism would produce an analgesic effect. Contradictory evidence of adenosine antagonism has also been reported at the supraspinal level as well. Regardless, the subjective data listed above indicates caffeine ingestion has an analgesic affect which would support, in part of the ergogenic effect of caffeine especially in regards to increased endurance.

Effects of Caffeine Ingestion on Motor Recruitment

Modification of motor recruitment both at the spinal and supraspinal level have been implicated as an ergogenic effect of caffeine. Caffeine is known to affect the central nervous system (CNS) by antagonizing adenosine receptor sites (Davis, 2003; Fredholm et al., 1999; Gandevia, 2006; J. James, 2005; Kalmar, 2005; Soto et al., 1994). Adenosine is an endogenous neuromodulator that exerts an inhibitory influence in the CNS. It decreases excitatory neurotransmitter release and firing rates of central neurons (Kalmar, 2005). Caffeine and adenosine are molecules that are similar in structure; hence, caffeine competes for binding sites with adenosine and nullifies the inhibitory effects of adenosine (Fredholm et al., 1999; Kalmar, 2005). From the schematic in Figure 2 antagonism of adenosine receptors by caffeine can occur at very low concentrations (<10μM) making it the most likely mechanism of caffeine ergogenic properties (Fredholm et al., 1999).

Evidence supporting caffeine-induced modulation of motor recruitment is yielded from research that has used neurophysiological techniques such as transcranial magnetic stimulation (TMS), twitch interpolation, and the Hoffmann reflex (H-reflex) to determine central and spinal excitability, as well as, maximal voluntary activation.

Central Excitability

TMS activates corticospinal motor neurons presynaptically, resulting in a motor evoked potential (MEP) that is recorded from the muscle usually be electromyography

(EMG). The amplitude of the MEP provides an estimate of central excitability (Kalmar, 2005). When eight TMS stimuli was applied at a rate of 0.3Hz and an output 15% of maximal stimulator output higher than resting motor threshold, 6mg/kg of caffeine did not increase amplitude of the MEP of the first dorsal interosseous measured 1h after ingestion (Kalmar & Cafarelli, 2004b). However, caffeine did increase in MEP amplitude at the beginning of a fatigue protocol but before fatigue (TMS was applied during the rest period in between sets of the fatiguing protocol) (Kalmar & Cafarelli, 2004b; Kalmar, 2005). Because caffeine increased MEP early in the fatigue protocol, the authors argue that potentiation of the MEP following non-exhaustive muscular effort; caffeine may exert its ergogenic effect by enhancing cortical facilitation during muscular effort (Kalmar & Cafarelli, 2004b). To test this hypothesis the authors conducted a similar study in the vastus lateralis muscle. Ten TMS stimuli was administered 1hr after 6mg/kg caffeine ingestion at the same rate and 10% of maximal stimulator output higher than active motor threshold (TMS was applied to subjects during a 3% MVC). Paradoxically, there was no difference in MEP between placebo and caffeine trials ($P = 0.055$), but a difference ($P < 0.05$) was measured between pre and post caffeine ingestion tests (Kalmar & Cafarelli, 2006). However, during magnetic stimulation of the motor cortex during a muscle fatiguing protocol, an increase in superimposed MEP amplitude and cortical silent period duration was observed (Kalmar & Cafarelli, 2006). These data indicate that caffeine induces a concurrent increase in excitability of the motor cortical neuron and cortical inhibition strengthening their earlier hypothesis (Kalmar & Cafarelli, 2006). The above data suggests that the effects of caffeine on MEP amplitude and the cortically evoked twitch are most likely due to central mechanism involving greater cortical facilitation during muscular effort (Kalmar & Cafarelli, 2006).

Adenosine is an endogenous inhibitory modulator for neuronal excitability and synapse transmission, as well as, an inhibitor of release of most brain excitatory neurotransmitters, particularly dopamine and may reduce dopamine synthesis (Davis, 2003). Caffeine-induced antagonism would increase dopaminergic activity, suggesting that dopamine's effects on arousal, motivation, and motor performance may contribute to the ergogenic effects of caffeine (Kalmar & Cafarelli, 2006). However, adenosine concentrations have not been measured in the brain during exercise, it is only known that adenosine levels are raised in working muscles and in the blood, as a result, and this mechanism is only speculative (Davis, 2003). Because, adenosine A_{2A} receptors are found to be concentrated in the dopamine-rich regions of the brain, caffeine increases dopaminergic transmission via postsynaptic mechanism by a blockade of A_{2A} receptors, while increasing neurotransmitter release and firing rates via A_1 receptor antagonism (Fredholm et al., 1999).

Spinal Effects of Caffeine

The effects of caffeine on motor unit excitability are equivocal. The most common research technique used to assess the effects of caffeine on spinal excitability has been the H-reflex. The H-reflex is an induced muscle contraction caused by electrical stimulation of a peripheral mixed nerve (a nerve that contains both afferent and efferent axons) (Zehr, 2002). The electrical stimulation will result in a direct efferent motor response (known as the M wave) and activation of the Ia afferents that innervate the muscle spindle sensory receptors resulting in an afferent volley that depolarize an αmotor neuron (α-MN) which will trigger contraction of muscle fibers innervated by that α-MN. The ensuing electromyography (EMG) reading is the H-reflex (Zehr, 2002). The earlier studies of caffeine ingestion that use the H-reflex technique (on the soleus muscle) to assess α-MN excitability found no effect (Kalmar, 1999; Kalmar, 2005). However, the application of the H-reflex by Kalmar & Cafarelli in their 1999 study was not ideal. Kalmar & Cafarelli analyzed maximal H reflex (H_{max}), which is a single point on the H-reflex recruitment curve, as the sole estimate of α-MN pool excitability (Kalmar, 2005). The authors did not consider the fact that presynaptic inhibition of monosynaptic spinal reflexes which make it difficult to interpret changes in H-reflex size as changes in α-MN excitability, because presynaptic inhibition can alter the afferent volley evoked by the electrical stimulus subsequently altering the H-reflex leading to a false estimation of α-MN excitability (Zehr, 2002). To better investigate the effects of caffeine on spinal excitability Walton et al., 2003 recorded soleus H-reflex recruitment curves pre-post ingestion and analyzed the ratio between the slope of the H-reflex (H_{slope}) and the slope of the M-wave (M_{slope}). By evaluating H_{slope} / M_{slope} the data would not likely be skewed by the variations in H_{max} caused by collisions of input from the afferent to the α-MN (orthodromic flow) and depolarization of the motor axon at the site of stimulation (antidromic flow) (Walton et al., 2003). It has been suggested that at rest H_{slope} / M_{slope} of H-reflex recruitment curve is a better methodological tool to measure excitability of a motor neuron pool (Kalmar, 2005). Caffeine ingestion increased spinal excitability (Hslp/Mslp) 43+/- 17% (Walton et al., 2003). Caffeine ingestion increased H_{slope} and the ratio H_{slope} / M_{slope} such that H_{max} is reached at lower stimulus intensity, hence, the change in slope indicates motor unit excitability. Unfortunately, the H-reflex technique does not identify the mechanism by which motor neuronal excitability is altered, because α-MN excitability or the chance that an excitatory postsynaptic potential of a given intensity will result in an action potential is dependent on the sum of all synaptic input of the motor neuron as well as the membrane properties (Kalmar, 2005).

It is possible that caffeine increased H_{slope} / M_{slope} by antagonizing A_1 & A_2 receptors increasing serotonin concentration in serotonergic neurons of the raphe nuclei which have excitatory projections to spinal motor neurons, thus increasing spinal activity could be attributed to an increase in descending serotonergic input (Walton et al., 2003). Furthermore, caffeine increases serotonin concentration in supraspinal centers that input on the spinal cord, increase firing rates of noradrenergic neurons, increases dopamine release, thus it is possible that the production of the plateau potentials which shift resting membrane potential toward threshold may contribute to the increase in spinal motor neuron output (Walton et al., 2003). Conversely, H-reflex is also affected by presynaptic inhibition, thus, it is possible that caffeine has an effect on the presynaptic inhibition of an Ia afferent (Zehr, 2002).

Voluntary Activation

Caffeine also increases voluntary activation of motor units most like due to spinal and supraspinal modulation (Kalmar, 1999; Kalmar & Cafarelli, 2004a; Kalmar & Cafarelli, 2004b; Kalmar & Cafarelli, 2006). Voluntary activation determined by participants conducting isometric MVC with supramaximal pulses delivered during and immediately after the contraction. Maximal activation is then calculated from the size of the twitches evoked from the stimuli; this is known as twitch interpolation (Kalmar, 1999; Kalmar & Cafarelli, 2004b; Kalmar & Cafarelli, 2006). It should be noted however, that a twitch-like increment of force that is obtained with stimulation of a nerve that innervates only a part of whatever muscles are being studied, suboptimal motor neuron output is obvious, however, quantification of the level of output to a whole muscle group is more complex (Gandevia, 2006). Many motor nerves innervate the bulk of synergists and antagonists in a particular task (e.g. stimulation of common peroneal nerve contracts ankle dorsi and some plantar flexors, stimulation of femoral nerve activates knee extensors but also 2 weak knee flexors), hence, the size of the superimposed twitch can be contaminated by unwanted force by antagonists and voluntary activation is artificially high (Gandevia, 2006). The studies that have observed increases in maximal voluntary activation have used twitch interpolation by stimulation of the femoral nerve and the ulnar nerve. Stimulation of the ulnar nerve activates first dorsal interosseous and an antagonist adductor policis, as a result, the sensitivity of the twitch interpolation technique is limited in the studies reviewed (Kalmar, 1999; Kalmar & Cafarelli, 2004b; Kalmar & Cafarelli, 2006). The current hypothesis is that voluntary muscle activation may be modulated by alterations in voluntary or involuntary supraspinal input, the membrane properties of spinal motor neurons, as well as, afferent feedback to the spine or cortex. (Kalmar & Cafarelli, 2006) As stated above, caffeine may modulate all of these factors eliciting ergogenic effect of increased maximal voluntary activation of motor units.

Caffeine does affect the central nervous system by antagonizing adenosine receptors but the exact mechanisms of “how” adenosine antagonism enhances motor behaviour are still uncertain. The current evidence suggest that caffeine will increase voluntary activation of motor units via modulation of spinal and supraspinal excitability by affecting transmitter release (i.e. serotonin, dopamine, norepinephrine) and neuronal firing rates by means of blocking A_1 receptors (presynaptic effect) and increasing dopaminergic transmission by blocking A_{2A} receptors(postsynaptic effect). By reliving inhibitory affects of adenosine both spinally and supraspinally, caffeine seems to cause increased motor unit recruitment. Increased motor unit recruitment would explain increases in self-selected power outputs during time-trial based exercise tests (Doherty, 2004a; Doherty, 2004b). Likewise, a proportion of the ergogenic effects of caffeine can be contributed to superior motor unit recruitment.

Impairment to Exercise Caused by Breathing through the SCBA and Wearing PPE

Fire fighting is a unique physical occupation due to the external stresses experienced from both the environment and the safety equipment worn by firefighters during emergency situations. The micro-climate created by firefighter PPE and the resistance to breathing caused by a self-contained breathing apparatus (SCBA) are unique stresses in which the effect of caffeine on work tolerance is unknown. The micro-climate of firefighter PPE applies a distinctive heat stress by impeding the exchange of metabolic heat from the body into the atmosphere, thus increasing the risk of heat illness and injury when compared to most other occupations (Baker, 2000; Smith, 2001). In addition, the increased weight of equipment and it's affect on efficiency of exercise and work tolerance have been shown to elicit higher submaximal $\dot{V}O_2$, $\dot{V}_E$, and HR are in protective gear compared to regular exercise conditions (Dreger, 2006; Eves, Petersen, & Jones, 2003b). Firefighter PPE has an even greater effect during maximal exercise, reducing $\dot{V}O_{2max}$ by approximately 18% (Dreger, 2006). It is estimated that of the 18% reduction in $\dot{V}O_{2max}$, 4% of the reduction is due to firefighter protective clothing while the rest has been attributed to the resistance to breathing caused by the SCBA regulator (Dreger, 2006).

The main reason for decline is maximal exercise is the decrease in maximal $\dot{V}_E$ (Dreger, 2006). The exact cause of $\dot{V}_E$ limitation is unknown, however, recent research indicates that an increased work of breathing due to expiratory resistance caused by regulator in combination with impairment in thoracic excursions due to the weight of the SCBA harness are the leading factors (Dreger, 2006). The impairment of thoracic excursions has been studied during rest. The strapping effect of the SCBA harness and air cylinder has been shown to decrease vital capacity by 4%, chest wall compliance (20%), decrease (Expiratory Reserve Volume) ERV to decrease (10%) when compared with control conditions (Butcher et al., 2007). The authors conclude that for a given tidal volume, the reduction in the chest wall compliance in would increase the inspiratory elastic work of breathing (Butcher et al., 2007). Even though there is no direct measure data of chest wall compliance during exercise, these findings support the model of a reduced exercise capability caused by wearing a SCBA harness and air cylinder as a part of firefighter PPE.

Furthermore, exercise capacity is diminished by the effects of the SCBA regulator on ventilatory mechanics. During stepping exercise (80% of peak stepping rate), the SCBA increased total work of breathing (WOB) by 58 % (Butcher et al., 2007). However, in this study the increase WOB only occurred during the third and final 10min bout of the stepping exercise (each 10min exercise bout was separated by 5min of recovery). In this particular study, $\dot{V}_E$ only reached 100L/min or greater during the third work bout, which that laboratory has shown to be the point where SCBA regulatory resistance to have a greater affect on total WOB (Butcher, Jones, Eves, & Petersen, 2006; Butcher et al., 2007; Eves et al., 2005). Additionally, the authors discovered that exercising with the SCBA caused a relative increase in both inspiratory and expiratory muscle work (55% and 133%, respectively) (Butcher et al., 2007). The authors attributed the increase in inspiratory muscle work resulted from increased inspiratory elastic work (79%) while increased expiratory muscle work was derived from a 228% increase in expiratory resistive work (Butcher et al., 2007). These data implies that exercising with an SCBA can significantly impair ventilatory mechanics, pulmonary function and respiratory muscle strength when compared with low resistance breathing valves due to the combination of increased expiratory breathing resistance and increase increasing lung volumes (Butcher et al., 2007).

From the literature it is apparent that fire fighting is a physically demanding occupation with distinctive characteristics and challenges that may be affected by the use of caffeine. It is possible that caffeine's ergogenic effects on ventilation, perceived exertion and pain/discomfort may alter physiological variables allowing for a change in the body's tolerance to the unique physical demands of fire fighting.

Conclusions

The literature on the effects of caffeine on exercise is limited by the fact that only a few labs have conducted this type of research with respect to the neurological effects, especially in humans. Most of the work has been conducted by one lab at York University (by Cafarelli and Kalmar); however, there are some conclusions that can be made about caffeine's action on several aspects of exercise that may alter the work tolerance of firefighters. In humans, orally ingested caffeine that elicits plasma caffeine levels between 40-70 μM of caffeine can have an ergogenic effect by increasing motor unit recruitment, producing an analgesic affect on muscular contraction; lower the overall perception of exertion, causing a more efficient excitation-contraction coupling of muscle, increasing blood pressure without increasing HR or altering CHO and fat metabolism. The overall ergogenic effect of caffeine appears to be "a sum of the parts" rather than one predominate factor. Logic leads to the assumptions that modulations of motor recruitment and excitation-contraction coupling are more relevant to increases in power output, whereas, analgesia and lower RPE are more relevant to increased endurance time. Cardiovascular and metabolic alterations (i.e. increased arterial lactate concentration) have an unknown or remedial effect on the ergogenic properties of caffeine.

The mechanisms behind caffeine's ergogenic actions are antagonism of adenosine receptors, increased breathing efficiency, increased Ca^{2+} release, and K^+ reuptake. Adenosine antagonism both spinally and supraspinally; increases neuronal transmitter release (norepinephrine, dopamine, serotonin) and firing rates increasing in motor pathways, while inhibiting pain transmission and sensation via sensory pathways are responsible for the alterations in motor recruitment and analgesia. The direct effect of caffeine on RyR increasing Ca^{2+} stimulated Ca^{2+} release from the SR and caffeine directly acting (or indirectly acting via increased epinephrine levels) on the Na^+ /K^+ pump to maintain ion balance are responsible increased excitation-contraction coupling. All of the aforementioned actions would facilitate muscular contractions, efficiency of breathing and increase the capacity for humans to perform work, thus, lowering RPE and perhaps increasing work tolerance.

Appendix B – Rating of Perceived Exertion

Scale	Severity
0	Nothing At All
Very Very Slight	
1	Very Slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Very Very Severe
10	Maximum

Modified Borg Scale, From Burdon JGW, Juniper EF, Killian KJ, Hargrave FE, and Campbell EJM. (1982). The Perception of breathlessness in asthma. *American Review of Respiration Disease*. 126: 825-828.

Appendix C –Perceived Thermal Distress

1 = my body temperature is comfortable
2
3 = I am starting to get hot
4
5 = I am hot
6
7 = I am very hot
8
9 = the heat is unbearable