The Effect of Ingesting Caffeine, Ephedrine, and their Combination on Repeated Strength Performance

by

Harley Pasternak

A thesis submitted in conformity with the requirements for the degree of Master of Science in the Exercise Sciences Programme
School of Graduate Studies
Department of Community Health, University of Toronto

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Abstract

This study has investigated the effects of acute ingestion of caffeine (C) (4 mg·kg⁻¹), ephedrine (E) (0.8 mg·kg⁻¹), and their combination (C+E) on muscular endurance, using a double blind, repeated measures design. After ingesting either a placebo (P) or one of the three treatments cited above, 13 male subjects performed a weight training circuit consisting of three supersets of leg press (at 80% of 1RM to exhaustion) followed by bench press (at 70% 1RM to exhaustion). The mean number (±SD) of repetitions for leg press was significantly (p<0.05) higher after both the E (17.4±6.2) and C+E (19.8±7.3) treatments than after either C (14.3±6.4) or P (14.1±4.8), but in the first set only. Similarly, the ingestion of E (13.3±2.9) and of C+E (14.3±3.1) was followed by significantly higher repetitions for bench press than was the case with the ingestion of either C (12.4±2.7) or of P (12.7±3.1). The total weight lifted during all three sets, both for leg press and bench press, did not change significantly after any of the three treatments when compared to P. Systolic blood pressure, measured both pre-and post-exercise, showed an increase with C+E (156±29) and with E (150±14) as compared to C (141±16) and P (138±14). It was concluded that acute ingestion of C+E and E increases muscular endurance, but only during the first of multiple bouts of exercise.
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LIST OF ABBREVIATIONS

5-HT  5 - Hydroxytyptomine
ANOVA Analysis of Variance
CNS Central Nervous System
D Dopamine
1-RM One Repetition
MAOD Maximal Accumulated Oxygen Deficit
NE Norepinephrine
RPE Rate of Perceived Exertion
STHIX Short Term High Intensity Exercise
V02MAX Maximal Oxygen Uptake
WMAX Maximal Workload
WS Work Set
WT Canadian Forces Warrior Test
cAMP Cyclic Adenosine Monophosphate
FFA Free Fatty Acid
Chapter 1
Introduction

The use of performance-enhancing substances by athletes is not a contemporary phenomenon. Athletes purportedly resorted to such measures over 2000 years ago. The term *ergogenic*, which is derived from the Greek word for work [1], is defined as that which increases work or the potential for work [2]. While the use of ergogenic aids is most commonly associated with those who are involved in sports and exercise, industrial workers and military personnel have also been known to engage in such performance enhancing practices. Williams [3] devised five categories of ergogenic aids: physiological, psychological, mechanical, pharmacological, and nutritional. Nutritional ergogenic aids are defined as substances found either in the diet or in certain kinds of cells that humans ingest when attempting to improve their sport, exercise, or general physical performance.

Caffeine is a widely used nutritional ergogenic aid. Almost all caffeine comes from dietary sources, mainly coffee and tea [4]. The ergogenic properties of caffeine have been attributed to its stimulation of the central nervous system (CNS) and/or to an increase in energy metabolism in the periphery via adenosine receptor blockade, improved neuromuscular transmission, increased muscle contractility, and increased catecholamine levels [5]. Many studies have established that caffeine can prolong the time to exhaustion in prolonged continuous activity [6-8].

In contrast, very few studies have examined brief intense exercise (90-100% \( \text{VO}_2 \) max) following caffeine ingestion. Among those, results are equivocal. Some studies have found that caffeine ingestion produces no effect on short-term high intensity exercise performance. Other studies, however, have reported an ergogenic effect during
graded incremental exercise tests [9]. Equivocal test results have also been reported with respect to supramaximal intensity exercise. Doherty [10] recently reported that caffeine ingestion increased the capacity for anaerobic exercise and improved supramaximal-running performance. On the other hand, Williams et al. [11] reported that caffeine produced no effect either on maximal power output or on muscular endurance during short, maximal bouts of cycling. Similarly, Collomp et al. [12] found that caffeine ingestion failed to increase either peak power or total work completed during supramaximal intensity cycle exercise.

A common finding of in situ studies of isolated animal muscle models is that caffeine treatment increases muscle force generation when the muscle is electrically stimulated [13]. The majority of human studies, however, have reported that caffeine affects neither maximal voluntary nor involuntary muscle force generation [5]. Thus, it remains uncertain if the ingestion of caffeine alone enhances muscle strength in humans.

Ephedrine, a sympathomimetic drug, is both an alpha and -adrenergic agonist, and stimulates receptors in the CNS and peripheral tissues via the displacement of norepinephrine from the nerve ending binding sites to the extracellular fluid. Until recently, there were only two published studies of the effects of acute ephedrine ingestion on exercise performance [14, 15]. Both studies reported that neither ephedrine nor pseudoephedrine produced an ergogenic effect on exercise performance.

Recent investigations indicated that ingestion of caffeine in combination with ephedrine (C+E) significantly increases physical work capacity during high intensity exercise. Bell et al. [16] found that the ingestion of 5 mg·kg⁻¹ of caffeine (C) combined with 1 mg·kg⁻¹ of ephedrine (E) significantly prolonged cycle ergometer exercise time at
85% VO_2max. Bell et al. [17] also reported that following the ingestion of C+E, improvements were noted in the Canadian Forces Warrior Test times (3.2 km military performance test where individuals run wearing light “fighting order” weighing about 10 kg). In contrast, C+E ingestion did not affect the results of anaerobic performance tests, such as peak or mean power generated during supramaximal intensity cycle exercise (45s Wingate Test); nor did C+E affect the results of a test, lasting approximately 2 min, for anaerobic capacity [18].

No studies have been published on the effects of C+E on tests of muscular endurance. Bell et al. [16] speculated that the primary mechanism of action following the ingestion of C+E is the stimulation of the CNS. If this is indeed the case, then it is reasonable to assume that muscular endurance would be enhanced following C+E treatment, particularly during consecutive sets of standard strength training exercises, insofar as the level of CNS stimulation can directly influence the rate of muscle force fatigue during such exercise [19]. In light of these findings, the current research proposes to determine the effects of ingesting C+E on muscular endurance.

A combination of caffeine and ephedrine has been shown to decrease the rate of perceived exertion (RPE) during high intensity exhaustive exercise [16]. The authors speculated that C+E might delay central fatigue, perhaps by affecting neurotransmitter and/or opioid activity. For this reason, the present study has included a blood analysis for identifying catecholamines (epinephrine and norepinephrine), and the opioid β-endorphin.
Chapter 2
Literature Review

2.1 Caffeine

2.1.1 History

The use of caffeine by humans dates back to Paleolithic times. To capture its stimulant properties, the raw fruit of the coffee plant, Coffea arabica, was used to prepare very strong caffeinated beverages. It is widely accepted that the Turks were largely responsible for the early popularity of coffee [20].

Caffeine initially found its way to North America in the form of Chinese tea. After the Boston Tea Party of 1773, coffee became North America’s primary form of caffeine. Other common food sources of caffeine include chocolate, soft drinks (colas), and cocoa [21]. The content of caffeine found in dietary sources range from 40 to 180 mg·150 ml⁻¹ in coffee; from 24 to 50 mg·150 ml⁻¹ in tea; from 15 to 29 mg·ml⁻¹ in cola; from 2 to 7 mg·150 ml⁻¹ in cocoa, and from 1 to 36 mg·28g⁻¹ in chocolate [22].

Caffeine has been used clinically in the treatment of neonatal apnea, asthma, atopic dermatitis, and migraine headaches [1]. Recently, as a result of caffeine’s popularity, it has been added to various weight loss or ‘fat burning’ supplements as well as to various nutritional supplements purported to increase exercise performance. These include but are not limited to caffeinated water, caffeine gum, caffeine pills, oral caffeine spray, caffeinated carbohydrate gel, and caffeinated energy bars [23].

Worldwide caffeine consumption from all sources can be estimated to be around 75 mg·person⁻¹·day⁻¹ but reaches 225 mg·day⁻¹ in the US and Canada and more than 400 mg·person⁻¹·day⁻¹ in Sweden and Finland, where 80 to 100% of caffeine comes from
coffee alone. While daily consumption of caffeine in the UK is close to that of Sweden and Finland, in the UK 55% of caffeine consumption comes from tea, 43% from coffee, and the remaining 2% from colas [21].

2.1.2. Chemistry

Caffeine occurs naturally in 63 species of plants. Along with theophylline and theobromine, caffeine is part of a group of alkaloids called methylxanthines.

Caffeine is a 1,3,7-trimethylxanthine. The first methyl group accounts for the CNS stimulation, the methylation of position 3 is closely linked to diuresis, and the methyl group at position 7 correlates with cardiac stimulation [24].

2.1.3 Pharmacokinetics

Caffeine absorption from the gastrointestinal tract is rapid, reaching 99% in approximately 45 min. Peak plasma caffeine concentration is reached between 15 and 120 min after oral ingestion [25]. Graham and Spriet [8] measured a peak plasma caffeine concentration of 45 μmol·L⁻¹ one-hour after a dosage of 6 mg·kg⁻¹. Toxic effects of caffeine are observed at plasma concentrations of 200 μmol·L⁻¹, and plasma concentrations of 500 μmol·L⁻¹ are considered to be fatal [9]. For doses less than 10 mg·kg⁻¹, caffeine half-lives range from 2.5 to 4.5h in humans [26].

Caffeine is primarily degraded via hepatic metabolism and the resultant single methyl group xanthines and methyluric acids are eliminated in the urine. From 0.5 percent to 3.5 percent of ingested caffeine is excreted unchanged in the urine [27].

2.1.4 Mechanisms of Action

There are three dominant theories regarding caffeine's mechanisms of
action on skeletal muscle physiology. These include (1) the mobilization of intracellular calcium from the sarcoplasmic reticulum of skeletal muscle, (2) the increase of cyclic-3', 5'-adenosine monophosphate (cAMP) by the inhibition of phosphodiesterases in muscle and adipocytes, and (3) the competitive antagonism of adenosine receptors, primarily in the CNS [28].

2.1.4.1 Mobilization of Intracellular Calcium

It is well documented that caffeine can initiate and potentiate muscle contraction [29]. At a concentration of 1 to 2 μmol·L⁻¹, caffeine lowers the excitability threshold and prolongs duration of the active period of muscle contraction in vitro by the release of calcium from the sarcoplasmic reticulum [30], and by inhibiting the re-uptake of calcium by sarcoplasmic reticulum, making the ion more available for muscle contraction. Caffeine also increases twitch tension development in muscles by sensitizing the muscular contractile apparatus to the concentration of intracellular calcium[31].

In order to produce detectable effects on calcium shifts, a minimal concentration of 250 μmol·L⁻¹ of caffeine is necessary [13]. Caffeine’s toxicity at or above this level makes it unlikely that the mobilization of intracellular calcium represents an essential mechanism of caffeine action in vivo [13].

2.1.4.2 Inhibition of Phosphodiesterases

Caffeine has been shown to cause the body to increase fat oxidation and decrease carbohydrate oxidation [32]. Using caffeine and theophylline, Sutherland and colleagues observed that methylxanthines prevented the enzymatic breakdown of cAMP by inhibiting cyclic nucleotide phosphodiesterase [33]. Cyclic-3', 5'-adenosine monophosphate (cAMP) is involved in the control of glycogen metabolism and
peripheral lipolysis [32]. The resulting increase in cAMP levels lead to increased levels of free fatty acids (FFAs), and thus to a glycogen sparing effect during prolonged exercise.

This phenomenon has only been observed in vitro. Furthermore, extremely high dosages of caffeine are needed to elicit this response. Therefore, there is not a very strong link between phosphodiesterase inhibition and the physiological doses of caffeine used in vivo [34].

2.1.4.3 Adenosine Receptor Inhibition

Adenosine inhibits neurotransmitter release and neuronal firing rates by binding to receptors of the CNS [35], thereby inhibiting neuronal activity and the release of neurotransmitters, thus interfering with synaptic transmission [36]. There are four distinct adenosine receptors, A1, A2A, A2B, and A3. Although all are important, A1 and A2A are the two most often examined in caffeine research because they are activated at quite low levels of caffeine [21]. A1 receptors have a high affinity for adenosine whereas A2A receptors have a low affinity. Via these two types of receptors, adenosine regulates a number of physiological functions either by inhibition (in the case of A1 receptors) or by stimulation (in the case if A2 receptors) of adenylate cyclase. Caffeine exerts antagonist actions on these same types of receptors [37].

In contrast to the other two mechanisms of action described above, most of adenosine's effects on the CNS can be inhibited by doses of caffeine that are well within physiologically non-toxic levels, comparable to approximately two cups of coffee [38]. This dose of caffeine has no reported effect either on cAMP metabolism or on calcium flux in the sarcoplasmic reticulum. The administration of adenosine usually produces
effects antagonistic to those of caffeine. These include depression of neuron activity, inhibition of synaptic transmission, and release of neurotransmitters [39].

Costill et al. [32] proposed a “metabolic hypothesis” to explain the performance effects of caffeine, particularly during endurance exercise. Their hypothesis was that caffeine ingestion leads to an increase release of catecholamines from peripheral nerve terminals and/or the adrenal medulla; that the elevated catecholamine levels stimulate the release of FFA from adipose tissue, resulting in elevated FFA levels in the plasma. This results in greater fat oxidation in the working muscles because FFA oxidation rate is a direct function of blood flow and arterial FFA concentration. The end result, according to the authors, is a reduction in glycolysis and the utilization of endogenous glucose and glycogen [40].

Caffeine is a well-known stimulant of the CNS [39, 41], largely as a result of an increased release of acetylcholine which, in turn, leads both to greater motoneuron recruitment and frequency of potentials of the motor end plate.

2.1.5 Adverse Effects

Numerous adverse effects have been attributed to the use of caffeine. Nervousness, irritability, and insomnia result from the CNS stimulant effect and may occur in different individuals at doses at or above 400 mg [42]. Fatal poisoning by the ingestion of caffeine is rare. However, the acute lethal-dose of caffeine in adults appears to be about 5 to 10 g [21]. Other effects include gastrointestinal distress, transient hypertension, and tachycardia [43].

Although some evidence exists that caffeine can induce chromosomal abnormalities in plant and mammalian cells in vitro via the inhibition of DNA repair
processes, such abnormalities are observed only with caffeine concentrations that far exceed those that tend to follow the ingestion of any caffeine-containing food or beverage [44].

Numerous studies have examined possible deleterious effects of caffeine in the etiology of acute myocardial infarction. However, most evidence has failed to link caffeine ingestion with an increase incidence of coronary heart disease [45].

While there is epidemiological evidence to suggest that high volumes of coffee consumption are associated with cancer of the pancreas, kidney, and lower urinary tract [43], these studies could not directly implicate caffeine because of the other chemicals found in coffee. Furthermore, these studies fail to exclude other confounding factors such as smoking.

2.1.6 Caffeine and Exercise Performance

Caffeine has long been suspected as having the potential to increase exercise performance. However, literature on the effects of caffeine has been divided on this subject. As a result, there have been conflicting rulings issued by various national and international athletic committees regarding the legality of caffeine use prior to athletic events. In 1962, a study conducted among Italian athletes reported that caffeine was one of the most common doping agents used by athletes [46]. Officials at the 1970 Commonwealth games comprised the first international group to ban the use of caffeine at a concentration equal to 2 cups of coffee [47]. Two years later, at the 1972 Olympic games in Munich, caffeine was taken off the list of banned drugs since there did not seem to be sufficient scientific evidence to support banning it [48]. Since that time, the IOC has changed its mind and has once again placed caffeine back on the list of banned
substances. In 1984, Delbeke et al. [49] reported the existence of a dose-response curve for the ergogenic response from caffeine use. Conservatively, it has been suggested that urinary caffeine levels of 10 μg·mL⁻¹ probably indicated intentional caffeine ingestion for the purpose of increasing athletic performance. Subsequently, the IOC established a legal limit for caffeine at 12 μg·mL⁻¹ while the CIAU and NCAA established it at 15 μg/mL⁻¹ [50, 51]. It should be noted that these limits are extremely high and are only reached after 5 to 7 cups of coffee. Furthermore, almost every study that has reported performance benefits from caffeine used doses that were well within permitted limits [6-8, 40, 52, 53].

2.1.6.1 Caffeine and Aerobic Exercise

The initial interest in caffeine as an endurance ergogenic aid was stimulated by a study that examined the effect of ingesting 330 mg of caffeine 1h prior to cycling exhaustion at 80% of VO₂max [32]. The researchers reported an increased time to exhaustion (75 min vs. 96 min) with caffeine. A second study demonstrated that ingestion of 250 mg of caffeine was associated with a 20% increase in the amount of work performed over 2h [54]. These studies demonstrated an increased use of fat as an energy substrate along with a decrease in glucose metabolism. An increase in venous FFA concentrations and a decrease in the subjects' respiratory exchange ratios (RER) supported this result. Similar results were reported by Essig et al. [40]. Using a cycle ergometer and a 5 mg·kg⁻¹ dose of caffeine, the researchers found a significant increase in time to exhaustion, along with a 42% decrease in muscle glycogen use. Berglund and Hemmingsson [55] examined the effects of 6 mg·kg⁻¹ caffeine on 14 competitive cross-country skiers in a 20 km ski run. There were significant decreases in time needed to complete the run. Sasaki et al. [56] reported that an absolute caffeine dose of 300 mg
improved performance by 35% in subjects who ran at 80% VO2max (53 vs. 40 min). Fulco and associates [57] examined time to exhaustion on a cycle ergometer following a 40 km march. Twenty-three caffeine-naïve subjects each received 5 mg·kg⁻¹ of caffeine. Despite decreases in the rate of perceived exertion (RPE) with caffeine ingestion, there was no increase in performance. Butts and Crowell [58] found no increase in performance in males and females cycling at 75 % 1h after ingesting 300 mg of caffeine. Ganslen et al. [59] studied the performance of 5 subjects on a treadmill test. A dose of 200 mg of caffeine had no effect either on aerobic capacity or work. In a similar study by Hogervorst et al. [60], 100 or 250 mg of caffeine were administered on 5 separate trials to 3 trained subjects. During a treadmill run to exhaustion at a supramaximal intensity, no effects of caffeine on oxygen uptake or performance time were observed.

2.1.6.2 Caffeine and Short-Term, High Intensity Exercise (STHIX)

While much research has been carried out to examine the effects of caffeine on endurance exercise, there have been few investigations into the relation between caffeine and short-term (≤ 5 min) high-intensity (≥ 90% VO2max) exercise [38]. Also, somewhat of a dichotomy may be seen in the research examining caffeine's ergogenicity during short-term exercise. Most in vivo studies fail to support caffeine as an ergogenic aid during short-term exercise. However, the majority of in vitro studies clearly demonstrate a relationship between caffeine and increases in performance [61].

Several studies have utilized an in vitro / in situ model with isolated muscle preparations to establish a relationship between muscle force generation and fatigue, as well as to determine the interaction of caffeine with various muscle types. Much of this work has focused to date on caffeine's effects on calcium within the sarcoplasmic
reticulum. Macintosh and Gardner [62] found an increased release of Ca\textsuperscript{2+} by the sarcoplasmic reticulum (SR). Others have found that with a concentration of 1 to 2 $\mu$mol·L\textsuperscript{-1}, caffeine lowers the excitability threshold and prolongs duration of the active period of muscle contraction both by increasing the release of calcium by the SR and by inhibiting the uptake of calcium back into the SR [30]. Gulati et al. [63] and Sandow et al. [64] found caffeine to increase twitch tension development in muscle.

The majority of studies that have examined caffeine's effect on STHIX fail to support caffeine as an effective ergogenic aid. Greer et al. [65] had subjects perform four 30s Wingate tests with 4 min of rest after treatment with either 6 mg·kg\textsuperscript{-1} of caffeine or placebo. Their data failed to demonstrate a difference between the treatment and control groups. Perkins and Williams [66] found no significant effects of caffeine on time to exhaustion during high-intensity exercise on a cycle ergometer. In a similar study, Williams and colleagues found no improvements in time to fatigue, peak power, and total work [11]. Collomp et al. [67] found that ingestion of a caffeine dose of 5 mg·kg\textsuperscript{-1} did not increase peak power or total work in 6 subjects performing a 30s Wingate test. However, using a dose of 250 mg, the same investigators found a significant 7% improvement in the maximal power output that could be generated during a series of 6s sprints at varying force-velocity relationships [12]. In attempting to measure indirectly the effects that caffeine may have on anaerobic capacity, researchers have used many different tests in order to quantify caffeine's effect on STHIX.

Recently, the maximal accumulated oxygen deficit test (MAOD) has gained popularity because it is both easily reproducible and non-invasive [68]. Using this test, both Doherty et al. [69] and Jacobs et al. [18] found caffeine to increase MAOD with a
dose of 5 mg·kg⁻¹ and cycling intensities of 125% VO₂ max and 150% VO₂ max, respectively. Jackman and colleagues [70] gave subjects 6 mg·kg⁻¹ of caffeine and had them cycle on an ergometer for 2 min, rest for 6 min, cycle for 2 min, rest for 6 min, and then cycle to exhaustion. The subjects who ingested caffeine experienced a significant improvement (approximately 20%) in time to exhaustion. Wiles et al. [71] found 3000 mg of caffeine to decrease performance times in a 1500m run as well as sprint speeds following a second 1500m run at a constant speed. Using absolute caffeine doses of 250 mg, Anselme [72] and co-workers had subjects perform a series of 6 cycle sprints with 5 min in between. Results showed that caffeine led to a significant increase (7%) in maximal anaerobic power (Wₘₐₓ). Collomp et al. [73] examined the effects of an absolute dose of 250 mg of caffeine on cycle time to exhaustion at 100% VO₂ max. Those receiving caffeine were able to cycle for nearly 30 seconds longer before reaching fatigue.

2.1.7 Caffeine and Neurotransmitters

Although the primary action of caffeine may be to block adenosine receptors, this leads to secondary effects on many neurotransmitters, including norepinephrine and dopamine [8]. These effects, in turn, influence a large numbers of different physiological functions.

Although caffeine ingestion has been shown to increase cerebral concentrations of the neurotransmitter serotonin (S) and of its precursors, 5-HT and tryptophan [74], caffeine has also been shown to decrease the availability of serotonin post-synaptically [75]. This decrease, in turn, affects central functions under serotoninergic influence, including sleep mechanisms, motor function, and cerebral blood vessels.
While there is relatively little research on caffeine's effect on \( \beta \)-endorphin, what evidence does exist invariably shows a definite increase in plasma \( \beta \)-endorphin release with caffeine administration. Arnold et al. [76] examined the effects of caffeine on \( \beta \)-endorphin levels in rats. The infusion of caffeine (20 mg·kg\(^{-1}\)) via a chronic, indwelling intra-atrial cannula resulted in a prompt and sustained rise in plasma \( \beta \)-endorphin levels. Also using rats, Khalil and associates [77] found a significant increase in cortex \( \beta \)-endorphin levels with intraperitoneally administered caffeine (10 mg·kg\(^{-1}\)).

To determine whether caffeine stimulated \( \beta \)-endorphin release in preterm infants with apnea, 27 infants were treated orally with caffeine (10 mg·kg). Blood samples taken 30 min after caffeine administration revealed a significant increase in plasma \( \beta \)-endorphin concentration [56].

Although there is considerable controversy regarding the precise role of the endogenous opioid peptide \( \beta \)-endorphin in modulating pain perception, there is little question that it can elicit analgesia. Administration of \( \beta \)-endorphin into cerebrospinal fluid (CSF) or brain sites causes long lasting analgesia in man and rats [76].

Since caffeine increases \( \beta \)-endorphin release [68], it is not surprising that many analgesic medications contain caffeine [76].

Researchers in the exercise sciences have recently increased their focus on the possible relationship between \( \beta \)-endorphin and exercise performance. It has been demonstrated that exercise-associated increases in \( \beta \)-endorphin levels are associated with changes in mood states and pain perception [78]. This finding made it possible to assign well-known sports-related phenomena, such as exercise induced analgesia and euphoria ("runner's high"), to a biochemical substrate. In light of this finding, It is speculated that
a potential mechanism of action for C+E, one that has not yet been investigated, may be related to a ‘dulling’ of the perception of fatigue as a result of a caffeine-induced increase in β-endorphin levels.

2.2 Ephedrine

2.2.1 History

Ephedrine hydrochloride is fast becoming one of the most used (and abused) drugs in sport and exercise today [23]. This CNS stimulant is available over the counter without a prescription. The emergence of ephedrine hydrochloride as potential drug of abuse dates back to the early 1970s, coincident with the controls placed on amphetamines by the Controlled Substance Act of 1970 in the United States [79]. To circumvent the intent of this act, ‘look-alike’ stimulants were formulated and marketed and were referred to, respectively, as black beauties, white crosses, and Christmas trees [80]. While various kinds of ingredients were to be found in such ‘legal’ stimulants, ephedrine invariably was the main component [1].

Ephedrine has been used in the past to treat Stokes-Adams attacks. It was also given as a CNS stimulant in cases of narcolepsy and for depressive states. Alternative modes for treating for such conditions have since been developed. In addition, the use of ephedrine as a bronchodilator for asthma patients has become much less extensive with the development of selective β2-agonists. Ephedrine has also been used to treat hypotension that sometimes occurs with spinal anesthesia [1]. Perhaps the most common modern day clinical application of ephedrine, one that is usually in the form of pseudoephedrine, is that of a sinus decongestant. Recently, a great deal of evidence has amassed supporting the use of ephedrine as an effective treatment for obesity. Research has shown
ephedrine to increase energy expenditure and lipolysis and to decrease appetite [81].

As of 1997, the United States Food and Drug Administration (USFDA) has collected over 125 dietary supplements labeled as containing a known source of ephedrine alkaloids [1]. These products, usually in the form of pills, capsules, powders, and liquids, often include caffeine and are marketed as “fat-burners” or “energy-boosters”.

Ephedrine is a substance banned by the International Olympic Committee (IOC) and most other international athletic governing bodies. Many athletes who have tested positive for ephedrine use have been suspended or expelled from international competition. Among these are Rick DeMont (Swimming, 1972), Juan De La Cruz (Track and Field, 1983), Diego Maradonna (Soccer, 1994), and Silken Laumann (Rowing, 1995) [1].

2.2.2 Chemistry

Ephedrine is a sympathomimetic amine. β-Phenylethylamine is generally considered the parent compound of most sympathomimetic amines, including ephedrine. Consisting of a benzene ring and an ethylamine side chain, ephedrine differs from other sympathomimetic amines owing to the presence of a hydroxyl group in the β position and a methyl substitution on the terminal amino group [82]. The substitution of the hydroxyl group on the β-carbon decreases lipid solubility, thereby decreasing both penetration into the brain and central stimulatory effects [82]. Only L-ephedrine and racemic ephedrine are used clinically.

2.2.3 Pharmacokinetics

Ephedrine is available clinically in a parenteral formulation for subcutaneous,
intramuscular, or slow intravenous administration. The drug is also available for clinical use in over the counter oral and nasal formulations for colds and allergies [1].

The clinical effects of ephedrine appear as early as 30 min after ingestion and can last up to 3 h. Time released oral and nasal decongestants can produce a clinical effect for 12 to 16 h. Ephedrine is rapidly absorbed and produces peak blood levels in 1 to 2 h. Although some ephedrine is metabolized in the liver, most is excreted unchanged in the urine. The half-life of ephedrine is 3 to 6 h. Typical clinical dosages of ephedrine range from 15 to 75 mg [83].

2.2.4 Mechanism of Action

Ephedrine exerts its effect indirectly on the CNS by displacing norepinephrine and other monoamine transmitters from storage sites [84]. The drug stimulates heart rate, cardiac output, and peripheral resistance. As a result, ephedrine increases blood pressure. Additionally, direct effects occur on both α and β-receptors [82]. Stimulation of the α-adrenergic receptors is responsible for nasal decongestion and for increasing the resistance to urine outflow (clinically applicable for incontinence). Activation of β-adrenergic receptors in the lungs promotes bronchodilation as well as thermogenesis, leading to fat loss in animals and obese humans [81].

Pseudoephedrine, a commonly used ephedrine alkaloid, is less potent than ephedrine both in its bronchodilatory and vasopressor effects. It produces about one-half the bronchodilation and one quarter of the vasopressor effects of ephedrine [85].

2.2.5 Adverse Effects

While most of the recorded side effects in the literature refer to pseudoephedrine use, it should be noted that ephedrine is far more potent. In fact, when compared to
pseudoephedrine, ephedrine has twice the half-life and bronchodilation effect and, in addition, produces three times greater vasopression [86]. Use of ephedrine has been reported to interfere with the regulation of serum potassium levels and thus may predispose certain individuals to cardiac arrhythmia, myocardial ischemia, and infarction [85]. Several studies showing the effects on blood pressure of ephedrine use have indicated that individuals with hypertension may be at greater risk of blood pressure elevations with use of the drug [87]. Adverse events associated with ephedrine-containing dietary supplements range from the clinically serious (such as chest pain, heart attack, stroke, hypertension, seizure, coma, psychosis, and death) to the less severe (nervousness, dizziness, tremor, minor alterations in blood pressure, headache, and gastrointestinal distress).

2.2.6 Ephedrine and Exercise Performance

There is very limited information on the effects of ephedrine on exercise. Using the ephedrine alkaloid, pseudoephedrine, Sidney and Lefcoe [14] had 21 subjects ingest either 24 mg of ephedrine or a placebo. Subjects were assessed for strength, endurance, power, VO_2max, reaction time, hand-eye coordination, anaerobic capacity, cardio-respiratory endurance, perceived exertion, and recovery time. The results indicated that pseudoephedrine had no effect on any of the performance variables measured.

Gilles et al. [15] measured whether a single dose of 120 mg pseudoephedrine ingested 120min before 1h of high intensity exercise influences performance. They failed to find an increase in isometric strength performance or a 40 km time trial on a cycle ergometer.

Twenty male cyclists (> 50 mi-wk⁻¹) were treated with either 1 mg·kg⁻¹ or
2 mg·kg⁻¹ dose of pseudoephedrine. The researchers failed to find a significant change in rating of perceived exertion (RPE), time to exhaustion, or VO₂max [88].

2.3 Caffeine and Ephedrine

2.3.1 History

The combination of caffeine and ephedrine has become one of the most popular performance cocktails in competitive sport and recreational exercise today [1]. The combining of caffeine and ephedrine is based on the speculation that caffeine induces a ‘permissive’ action of ephedrine, both lowering the threshold concentration required for physiological effects and potentiating the physiological effects of a given ephedrine concentration [81, 89].

It is postulated that the synergistic pharmacological effects of combining caffeine and ephedrine are attributed to an increase in CNS stimulation. Using rats trained to discriminate caffeine, ephedrine, or a combination of caffeine and ephedrine from saline in a two-lever drug discrimination procedure, Young et al. [90] reported that caffeine and ephedrine, in combination, mutually potentiated one another’s stimulus effect and resulted in a two-fold leftward shift over either ephedrine or caffeine alone in their respective dose-response curves. Vallerand et al. (1989) reported that the metabolic rate was significantly higher in resting shivering subjects after a combined caffeine and ephedrine treatment than with either caffeine or ephedrine alone. Similarly, Astrup et al. [81] reported similar results for average daily energy expenditure over several weeks in a clinical trial of combined caffeine and ephedrine used to treat obese individuals.

2.3.2 Caffeine and Ephedrine and Exercise Performance

To date, every published study that has examined the effects of combining
The first C+E study to come out of the DCIEM investigated the effects of acute ingestion of caffeine (C), ephedrine (E) and their combination (C+E) on time to exhaustion during high-intensity exercise. Using a repeated-measures, double blind design, eight male subjects exercised on a cycle ergometer at a power output that led to exhaustion after about 12.6 min during a placebo (P) control trial. They did this 1.5h after ingesting either C (5 mg·kg⁻¹), E (1 mg·kg⁻¹), C+E, or P. The combination of C+E significantly prolonged exercise time to exhaustion as compared to P, while neither C nor E treatments alone significantly changed time to exhaustion [16].

The next study was undertaken to investigate whether this enhancement would occur in a field setting, and if drug ingestion on 1d would affect performance 1d later. Two hours after ingesting either a combination of 375 mg of C and 75 mg E (C+E) or a placebo (P), 9 healthy male recreational runners completed six balanced and double-blind trials of the Canadian Forces Warrior Test (WT), a 3.2 km run wearing "fighting order" which weighed approximately 11 kg. The trials were performed in sets of two runs, conducted 24h apart. These sets were separated by a minimum of 7d. The sets were: C+E trial on day 1 (D1), placebo on day 2 (P2); placebo first (P1), C+E second (D2); and placebo first (P3), placebo second (P4). The two C+E trial run times were similar and both were significantly faster than control and all placebo trials. WT performance was not impaired by C+E ingestion 24h earlier. The authors concluded that performance of the WT was improved by ingestion of C+E [17].

In order to assess the effects of C+E ingestion on thermal regulation during
exercise in the heat, Bell et al. [91] had ten healthy male subjects exercise at 50% VO₂peak in a 40° C and 30% RH environment until rectal temperature reached 39.3°C or until they were thermally exhausted. Subjects performed four trials including a familiarization (F), control (C), placebo (P), and drug trial during which they ingested C+E (5 mg·kg⁻¹ and 1 mg·kg⁻¹ respectively). Tolerance times were similar for the P and C+E trials and both trials were significantly longer than the F and C trials. Although the metabolic rate was slightly increased with C+E treatment, it was sufficiently offset by increased heat loss mechanisms so that internal body temperature was not increased during moderate exercise in a hot, dry environment.

Bell et al. [16] had 24 subjects perform a maximum accumulated oxygen deficit test (MAOD), during which subjects cycled on an ergometer at 125% VO₂max to exhaustion. Ninety min prior to the test, the subjects ingested either C (5 mg·kg⁻¹), E (1 mg·kg⁻¹), a combination of C+E, or P. The results failed to reveal a significant increase in MAOD.

From the limited number of C+E exercise studies performed to date, it is known that the ingestion of C+E at approximately 4 mg·kg⁻¹ of C and 0.8 mg·kg⁻¹ of E can lead to an increase in both prolonged and high-intensity aerobic activity but not in high-intensity short-term exercise. To date, no one has examined the effects of C+E on muscular strength and endurance. Therefore, the authors intend to examine the acute effects of C+E ingestion on muscular endurance.
Chapter 3
Study Objectives and Hypotheses

3.1 Objectives

While the efficacy as an ergogenic aid of caffeine combined with ephedrine is well supported for prolonged bouts of exercise greater than 20min [16, 17], no research has been performed which examines the effects C+E has on short, high intensity exercise, such as resistance training. Furthermore, the documented ergogenic effects of C+E on aerobic exercise are the result of mechanisms that as yet are unknown. Bell et al. [17] have hypothesized that the central fatigue system may be involved and that C+E may influence the system by altering the production of various neurotransmitters.

Thus, the objectives of the present study were:

1. to examine the effects of C+E on muscular endurance
2. to determine the effects that C+E have on the neurotransmitter β-endorphin

3.2 Hypotheses

The hypotheses tested in this study are as follows:

3. C+E will significantly increase muscular endurance
4. C+E will cause an increase in plasma β-endorphin levels
Chapter 4  
Materials and Methods

This study was performed at the Defence and Civil Institute of Environmental Medicine (DCIEM) from November 1998 to June 1999. The study was approved by the Institutional Ethics committees both of the DCIEM and of the University of Toronto. The approved experimental protocol and ethics committee letter of approval are attached in the Appendices.

4.1 Subjects

Volunteer subjects consisted of civilian and military personnel from DCIEM, students from universities and high schools, as well as members of local fitness clubs.

Thirteen healthy, moderately active, male subjects, 18-34y of age, and familiar with weight training participated in this study. The mean height and weight of the subjects were 176 cm and 72 kg, respectively. It was decided beforehand not to include female subjects because the effects of a combination of caffeine and ephedrine on a fetus are unknown, and it was felt that the inadvertent exposure of a fetus to these drugs constituted an unacceptable and avoidable risk.

On the first visit, the experimental protocol was explained to each subject. Before completing and signing an ‘informed consent’ form and an ‘invasive procedures consent’ form, subjects were given the opportunity to ask questions about the protocol, as well as about any potential risks relating to the study. Subjects were also required to complete a medical screening questionnaire and were examined by a DCIEM physician to assure their suitability to participate in the study. They were also required to abstain from consuming coffee, alcohol, and any other stimulative substances for 48h before each trial
for the duration of the study. In addition, they were instructed to maintain their normal exercise regime, but to avoid any hard exercise 24h prior to each visit. All subjects were non-smokers.

4.2 Experimental Protocol

The experiment consisted of nine visits. In the first session, medical screening was followed by a one-repetition maximum (1RM) assessment for both leg press and bench press. The second and third sessions were familiarization trials during which the subjects would become familiar with the equipment, schedule, and catheter. Sessions four through eight were the treatment trials and session nine was a re-assessment of the subjects' 1RM. Testing was performed on a Smith Machine bench press (Atlantis, ASE-155) and a plate loaded 45-degree angle leg press (Atlantis, ASC-101). The leg press seat height, headrest position, and range of motion (marked using small rubber hose segments) were measured during the first session for each subject and were kept at the same measurements throughout the study.

4.2.1 Session 1

Subjects arrived at the DCIEM and were briefed on the details of the study. After the subjects had sufficient time to read and sign the consent forms, they underwent a medical screening that included a resting 12-lead electrocardiogram evaluation. Following approval of medical fitness to participate by a DCIEM physician, the subject was familiarized with the strength training equipment.

One repetition maximum (1RM) refers to the force that a muscle or muscle group can exert against a resistance in one maximal effort [92]. Due to a multitude of factors, mainly related to safety, it was decided that we would assess the subjects' ≤10RM (the
amount of weight lifted for a maximum of ten repetitions) and extrapolate the findings to reach the corresponding 1RM. Determination of 1-RM for upper and lower body was assessed using a smith machine bench press and plate loaded leg press, respectively (see Appendix I). Before the subject began, they were asked to place themselves in the “lifting position” for both exercises. This allowed the researchers to properly determine the proper bench position (bench press), head rest, back rest, and range of motion (leg press) that would best suit the subject. Range of motion on bench press was measured as having the subject lower the bar to their chest (without bouncing it off their chest) then pressing it up until they have reached full elbow flexion. Range of motion on leg press was measured as a subjects going from 90°- angle knee flexion followed by full knee extension. In order to insure that the range of motion was consistent for each subject in each trial, small rubber hose segment were placed along the leg press tracks (upon which the plate loaded platform slid up and down) to mark the bottom of the range of motion.

After a light warm up of 10 repetitions at one-third bodyweight for bench press and an amount equal to the subject’s body weight for leg press, the test began. The ≤10RM was determined through the trial and error method. If an attempt was made with relative ease, 25-50% more weight was added to the resistance. The two exercises were performed without any rest time between them, as subjects received a 2min rest period between supersets. Repetitions for each lift were done using a continual cadence (i.e. no pause at the end of each repetition). Once the subject performed a set with a weight with which they could do no more than ten repetitions, the weight used and number of repetitions performed were extrapolated to a 1RM using a 1RM table (see Appendix G) [93].
There were two key factors in the decision to use resistance machines over free
weight equipment. Free-weights are influenced by a motor learning factor (i.e., balance
and coordination), which is far less critical with machines. Furthermore, given the
rigidity of a resistance machine’s range of motion (ROM), there is less of a chance for
injury than there is with free-weight equipment.

Bench press and leg presses were selected as exercises to represent upper and
lower body respectively, due to the large muscle mass each exercise recruits. Bench press
utilizes the pectoralis muscles as well as the shoulder and triceps muscles. Leg press
demands the contraction of most of the muscles in the lower body, including the
quadriceps, gluteus, and hamstring muscles.

4.2.2 Session 2

Approximately one week after session 1, the subjects underwent the first of two
familiarization trials. Using the data from the subjects’ 1RM test, 70% and 80% of 1RM
for bench press and leg press, respectively, were calculated. These numbers were selected
based on previous studies, which found that the 10RM are performed somewhere
between 60 and 80 percent of the 1RM [94]. Furthermore, our pilot study found that
subjects were able to do more repetitions at a given percentage of 1RM with the lower
body than with the upper body. Therefore, subjects performed leg press with 80% of
1RM and bench press with 70% 1RM.

The subjects reported to the lab in the morning in a fasted but well hydrated state.
They were given a standardized meal of two starch servings and a 357 mL bottle of fruit
juice. Starch choices included white toast, muffins, or bagels. Approximately 30min after
consuming the meal, the subject began to warm-up. The warm up consisted of one
superset (the execution of two exercises in succession without a rest) between leg and bench press at 40% 1RM and 35% 1RM, respectively. After 2min rest the subjects began the actual work set (WS). The WS consisted of three supersets, with each superset consisting of leg press followed by bench press, with two mg·kg of rest between each set. The leg press had a resistance equal to 80% of 1RM and the bench press 70% of 1RM. Each set was done using a constant cadence, full range of motion (ROM) (measured with rubber hose segments placed along the tracks upon which weights slide), and was taken to muscular failure.

4.2.3 Session 3

Approximately one week after session 2, the subjects arrived at the DCIEM in a fasted state. Immediately after arriving, they received the same standardized meal given in session 1. Fifteen mg·kg after the meal, and to familiarize them with the procedure, subjects who had not previously participated in experiments involving catheterization had a venous catheter inserted into a superficial forearm vein. A 5 L blood sample was taken to ensure subjects would not experience a vaso-vagal reflex. After-

15 mi of sitting, blood pressure was taken followed by removal of the catheter. Immediately after, the subjects began to warm up and begin their WS as in session 2.

4.2.4 Session 4-8

Approximately one week following session 3, subjects began their treatment trials. Each of the five trials was done at the same time of the day and week with one week in between trials. These trials were identical to session 3 except that the subjects ingested gelatin capsules immediately upon arriving at the DCIEM. The capsules contained one of the following treatments: C (4.0 mg·kg\(^{-1}\) bodyweight), E (0.8 mg·kg\(^{-1}\)),

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C+E, or placebo (P) (Metamucil©). Of the five trials, two were placebos. The order of treatment trials was randomized among the subjects. The time course of events for these trials, using arrival time as the reference time zero, was as follows:

**Time 0 (zero) – arrive and ingest treatment capsules**

**Time 15 min – complete standardized breakfast**

**Time 30 min – change into exercise clothing and insert venous catheter**

**Time 65 min – begin seated rest period prior to blood sampling**

**Time 85 min – blood sampling followed by blood pressure measurement**

**Time 90 min – commence warm-up**

4.2.5 Session 9

Session 9 was the same as session 2 with a re-assessment of the subject's 1-RM. This was done to ensure that any performance increases were not due to a training effect.

4.3 Measurements

4.3.1 Blood Pressure (BP)

BP was measured 85min after ingesting the treatment, just before the catheter was removed and the subject began to exercise. Measurements were taken manually with a sphygmomanometer and with the subject sitting on a chair. The right arm was used for all measurements.

4.3.2 One-Repetition Maximum (1-RM)

This refers to the maximal resistance that can be lifted for one repetition. Interpolating the results from the subjects' 10-RM using a 1-RM chart [94](see appendix F) attained the 1-RM.
4.3.3 Ten-Repetition Maximum (10-RM)

This refers to the maximal resistance that can be lifted for ten repetitions.

4.3.4 %-Fatigue

This refers to a measurement of recovery between sets and the effect of a set or sets on future sets. It is calculated by dividing the number of repetitions in one set by those in a previous set then multiplying by 100.

(i.e. %-Fatigue_{set2-set1} = \frac{\text{set 2}}{\text{set 1}} \times 100)

4.4 Biochemical Assays for Metabolite, Catecholamine, and β-endorphins

4.4.1 Blood Sampling and Collection

Blood was drawn through a Teflon catheter (Dessert Medical Inc., Sandy, UT) inserted into an antecubital vein. The catheter was kept patent with a heparin lock (0.25 mL of heparin (10 units/mL)). Venous blood samples (10 mL) were collected in 2 vacutainer tubes (one for the determination of catecholamines and caffeine and ephedrine metabolites; the other for β-endorphins). These tubes were immediately centrifuged at 10° C for 15 min. After the centrifuge, the plasma component of the samples was separated, placed in clean 5 mL polystyrene tubes, and stored at -70° C until the samples were analyzed.

The plasma samples were assayed for norepinephrine, epinephrine, ephedrine, caffeine, and β-endorphin (See Appendix D)
4.5 Data Analyses

4.5.1 Analysis of Variance (ANOVA)

All ANOVAs were performed using statistical software Super ANOVA v1.11, (Abacus Concepts Inc., Berkeley California or SAS®, Version 5, 1991 by SAS Institute Inc. Cary, NC, U.S.A) on a Macintosh personal computer.

A two-factor repeated measures analysis of variance (AN) was used to determine the significance of total work done (repetitions x resistance) among the treatment trials.

4.5.2 Power Analysis

An a priori statistical power analysis for number of repetitions was performed. Prior to the study, it was decided that a definite drug effect would have to be at least equivalent to the effects of 6 weeks of strength training. According to the literature, this number is an increase of approximately 30% in repetitions performed [81,82]. An estimation of the required number of subjects to achieve a power of 0.8 was carried out following power calculations. The required number of subjects for the power of 0.8 was ≈ 12 subjects.
5.1 Plasma Caffeine and Ephedrine Concentrations

Blood samples for plasma caffeine and ephedrine measurements were taken just before exercise, 90 min after ingestion of the treatment (Figure 1). Caffeine values were almost identical both for C (6848± ng·mL⁻¹) and for C+E (6594± ng·mL⁻¹). Similarly, plasma ephedrine levels were very close both for E (301± ng·mL⁻¹) and for C+E (295± ng·mL⁻¹) treatments. No caffeine or ephedrine was detectable during the placebo trials.

![Caffeine Graph](image)

![Ephedrine Graph](image)

Figure 1: The effect of Caffeine (C), Ephedrine (E), and C+E (CE) on plasma levels of either caffeine or ephedrine. [Shown are the results of one-way repeated measure ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (** p<0.01 vs. placebo). Data are means ± SE; n = 13.]
5.2 Order Effect

No significant order effect was found for exercise to exhaustions among days for total upper and lower body. (Figure 2).

Figure 2: Order Effect – Combined upper and lower body. Data are means ± S.E.; n = 13.
5.3. Lower and Upper Body Muscular Endurance

The mean number (±SD) of repetitions for leg press was significantly (p<0.05) higher after both the C+E (19.8±7.3) and E (17.4±6.2) treatments compared to both C (14.3±6.4) and P (14.1±4.8) in the first set only (Figure 3). Similarly, both C+E (14.3 ±3.1) and E (13.3±2.9) led to significantly higher repetitions with bench press when compared to C (12.4±2.7) and P (12.7±3.1) (Figure 4). Total weight lifted during all three sets for both leg press and bench press was not significantly changed by any of the treatments compared to P.

Figure 3. The effect of Caffeine (C), Ephedrine (E), and C+E on Upper Body Muscular Endurance. [Shown are the results of 2-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (** p<0.01). Data are mean ± SD; n = 13].
Figure 4. The Effect of Caffeine (C), Ephedrine (E), and C + E on Lower Body Muscular Endurance. [Shown are the results of 2-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (** p<0.01). Data are mean ± SD; n = 13].
5.4. Lower and Upper Body Muscular % Fatigue

There was a significant main effect for % fatigue between set 1 and set 3 (P<0.001), set 2 and set 3 (P<0.001), but not between set 1 and set 2 (P>0.05) for upper body. The % fatigue between set 1 and set 3 was significantly different in C+E or E versus placebo. All the treatments proved to be significantly different versus placebo for % fatigue between set 2 and set 3.

**Figure 5. The Effect of Caffeine (C), Ephedrine (E), and C + E on between set upper body % fatigue. [Shown are the results of one-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (* p<0.05, ** p<0.01). Data are mean ± SE; n = 13].**
There was no main effect of the drug on % fatigue between any of the sets for the lower body.

Figure 6. The effect of Caffeine (C), Ephedrine (E), and C + E on between set lower body % fatigue. [Shown are the results of one-way RM ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (* p<0.05, ** p<0.01). Data are mean ± SE; n = 13.]
5.5 Blood Pressure

Systolic blood pressure measured just prior to exercise was increased with C+E (156±29) and E (150±14) compared to C (141±16) and P (138±14). Diastolic blood pressure was not significantly different among trials (Figure 7). One of the subjects displayed an abnormally high hypertensive response to caffeine and ephedrine. The subject, a healthy, normo-tensive 21yr old, had a resting blood pressure of 212/109 90min. after ingesting caffeine and ephedrine. After consulting with DCIEM medical staff, the researchers waited (approx. 10min) until the subject's blood pressure dropped slightly and continued with the trial under the supervision of a physician.

Figure 7: The effect of Caffeine (C), Ephedrine (E), and C + E on systolic and diastolic blood pressure. [Shown are the results of one-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (** p<0.01 vs. placebo). Data are means ± SE: n =13].
5.6 Pre-exercise Plasma β-Endorphin

Ten of the thirteen subjects' samples were assayed for pre-exercise plasma β-endorphin. There was a significant (p<0.01) increase with C+E (6.5±5.0) when compared to all other treatments [E (0.4±3.5), C (2.4±2.1), and P (1.7±2.9)] (Figure 8)

![Graph showing plasma β-endorphin concentrations](image)

**Figure 8:** Resting concentrations of plasma β-endorphin 1h post-ingestion of treatment drug. [Shown are the results of one-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison (** p<0.01 vs. placebo). Data are means ± SE; n = 13].
5.7  Pre-exercise Plasma Epinephrine, Norepinephrine, and Dopamine

Evaluations of plasma catecholamines (E, NE, DA) were done on samples drawn 90 min after ingesting and just prior to exercise. There was no significant change in catecholamines with any of the treatments (Figure 9).

![Graph showing plasma catecholamines](image)

Figure 9: The effect of Caffeine (C), Epinephrine (E), and C + E on plasma levels of norepinephrine and epinephrine. [Shown are the effects of one-way repeated measures ANOVA (rectangular box) and Newman-Keuls post-hoc comparison. (** p<0.01 vs. placebo). Data are means ± SE; n = 13].
Chapter 6
Discussion

6.1 Review of Objectives and Hypotheses

The objectives of this study were to examine the effects, respectively, of caffeine, of ephedrine, and of caffeine and ephedrine combined, on upper and lower body muscular endurance, and to determine whether these treatments have an effect on various neurotransmitters, specifically β-endorphin.

There were two hypotheses tested in this study. The first stated that C+E would significantly increase muscular endurance, which would be demonstrated by more work being completed before exhaustion during the three supersets. This hypothesis was partially confirmed, as the results demonstrated an ergogenic effect for E and for C+E both for upper and lower body, but in the first set only. The second hypothesis was that C+E would cause an increase in plasma β-endorphin. Analysis of the plasma samples served to validate this.

Given the previous findings from Bell et al. [16], which established caffeine and ephedrine as an effective ergogenic aid both during high-intensity exhaustive exercise as well as prolonged endurance exercise, we thought that its efficacy in short-term, high-intensity exercise requiring local muscular endurance should be tested.

6.2 Main Findings

It was confirmed that C+E and E significantly increased both upper and lower body muscular endurance. Furthermore it was shown that C+E significantly increased plasma β-endorphin. These results contrast the negative findings of another C+E study at similar intensity and duration [16]. Using a cycle (and not weight machines), Bell et al.
[16], had 8 subjects perform 45s Wingate tests. They found a significant increase in performance with C and not with E or C+E.

While the possibility of skeletal muscle metabolism changes cannot be completely excluded, it is more plausible that the increase in muscular endurance with C+E was mediated by an increase in CNS stimulation and β-endorphin production, which may have masked some local muscular pain. These somehow postponed fatigue in the first set allowing the subjects to perform more repetitions before fatigue. However, it is difficult to explain why there was only a significant increase in β-endorphin production with C+E while there was an increase in performance with both C+E and E. Recent evidence suggests that there may be local factors involved. A study using tetraplegics reported a significant increase in muscular endurance with caffeine administration [95]. This could only be the result of local, not central factors. Furthermore, there may be a number of other neurotransmitters that could have had an effect on performance, but due to the relative infancy of central fatigue research, we cannot be sure.

As mentioned previously, it is unlikely that an increase in performance was due to metabolic factors. Due to the very nature (i.e. duration and intensity) of the weight training circuit, the ATP-CP system is dominant and neither anaerobic-glycolysis nor aerobic metabolism are limiting factors [19]. Therefore, the increase in performance was probably due to a number of factors, both central and peripheral.

Both lower and upper body experienced an increase in performance with C+E and E. However, the increase was more dramatic in the lower body. The author speculates that this is due to the larger muscle mass and greater number of muscles involved in the leg press compared to the bench press. The bench press uses only three major muscles
(pectoralis major, deltoids, and triceps) while the leg press uses many more (and larger) muscles such as the gluteus muscles (three), the quadriceps muscles (four), the hamstrings (three), and many more as these muscles fatigue [96].

As a result of performing more work in the first set with C+E compared to the other treatments, the subjects experienced more fatigue and a lesser ability to recover for the second and third sets (see figures 5.6). This phenomenon was present for both upper and lower body but was only significant for upper body. This may be due to the very large musculature of the lower body and its tendency to produce large amounts of lactic acid during exhaustive resistance exercise, affecting the ability to perform many repetitions in future sets [97].

While C and E are considered relatively benign drugs on their own, the US FDA has reported a number of adverse health effects, most of which were vascular in nature [85]. In light of this, the researchers decided to investigate the effects C+E have on blood pressure before suggesting these drugs to Canadian Forces personnel. There was a significant increase in systolic blood pressure with C+E (156±29) and E (150±14) compared to C (141±16) and P (138±14). This is consistent with Bell et al. [17] who found C+E to significantly increase systolic blood pressure (138±11) over C (126±10), E (132±10), and P (118±8) one hour after ingestion. Bordeleau et al. [98] also reported systolic values of for C+E (138±11) to be significantly greater than those for P (118±8).

The absence of any significant change in diastolic pressure with any of the treatments was in line with other studies [17, 98].

Biochemical analysis revealed pre-exercise, post-treatment (t=90 min) plasma caffeine levels to be almost identical for both C (6848.1 ng·mL⁻¹) and C+E
(6594.2 ng·mL\(^{-1}\)). Similarly, plasma ephedrine levels were almost identical for both E (301.3 ng·mL\(^{-1}\)) and C+E (295.7 ng·mL\(^{-1}\)) treatments. Thus, it appears that combining C with E has little influence on the rate of appearance/disappearance in plasma for the individual drugs compared to ingesting caffeine alone. No caffeine or ephedrine was detectable during the placebo trials. The mean plasma caffeine levels of all previous C+E studies from Bell et al. [15-20] are very similar.

Plasma was further analyzed for epinephrine, norepinephrine, dopamine, and β-endorphin. Examination of the data revealed no significant change in any of the catecholamines. This differs from the average plasma levels from previous C+E studies [15-20]. However, there was a significant (p<0.001) increase in plasma β-endorphin with C+E (6.50±5.01 pmol·L\(^{-1}\)) over C (2.36±2.10), E (0.42±3.46), P (1.67±2.87). This increase may be a factor in the ergogenic effect of C+E. β-endorphin has been implicated with positive mood changes. Furthermore, Berk et al. [99] suggested that endorphins might provide analgesic against exercise-derived pain. Haier et al. [100] demonstrated that exercise significantly lengthened the time to the first report of pain from a 1.4 kg force applied to the fingertip. Naloxone (a β-endorphin antagonist) administration completely blocked this exercise-induced analgesia. While many early studies failed to find a statistically significant physical relationship between central and peripheral β-endorphin levels [101], more recent evidence [102] in which β-endorphin levels in cerebrospinal fluids were measured after intravenous infusion of β-endorphin in humans. It should be noted that β-endorphins are only a small component of a larger family of similar molecules (enkaphalins) [65]. While β-endorphin was the only member of this family measured, it is entirely possible that other opioids may have been involved in the performance increase.
Chapter 7
Limitations, Conclusions, and Recommendations

7.1 Limitations

Several factors may have limited the validity or reliability of this study:

While this study was designed as a double-blind study, it is almost impossible to make the subject blind to the physiological effects of the drug treatments in the trial and, as a result, the researcher is aware both of the subjects’ behavior and blood pressure. This has the potential of biasing the subject and/or the researcher.

In exercising to failure, there is a large psychological component that differs between subjects. This component may impact upon variations in the ‘failure point’ both within and between subjects. This is perhaps most noticeable during the subjects’ 1-RM assessments.

The author, who is not an experienced researcher, did the analysis of the blood plasma for caffeine, ephedrine, catecholamines, and neurotransmitters. This may have caused the blood results to be slightly inaccurate.

7.2 Conclusions

The acute ingestion of either ephedrine alone, or in combination with caffeine, increases upper and lower body, high-intensity (70-80% 1-RM to exhaustion) muscular endurance, but only during the first bout of exercise involving multiple bouts.

The increased β-endorphin levels caused by C+E treatment are consistent with an effect mediated by CNS neurotransmitters.
7.3 Recommendations for Future Study

Directions for future study should include the following:

The mechanism of action for the ergogenic effect of C+E combination is still not clear. Perhaps, similar studies should examine its effect on central fatigue as well as any possible peripheral factors that may be affected by C+E ingestion. The use of tetraplegics subjects would be a useful tool in differentiating central from peripheral effects. Future studies should collect between-set plasma samples in order to measure both lactic acid and markers of acute exertional rhabdomyolysis. Such measures may shed some light on the ergogenic mechanism(s) and the extreme decline in subsequent performance with C+E.

The effect of C+E on cognitive function and mood state should be further investigated. These two areas are important, given that the military has considered using C+E in the field. More attention should be focused on all key neurotransmitters that may be involved in central fatigue, as well as on any other analgesic neurochemicals, such as β-endorphin, which may contribute to the delay of fatigue.

Field studies will be important in determining whether C+E would actually help the military in the field, using variables that were purposely excluded in lab research.
REFERENCES

15. Gillies, H., et al., Pseudoephedrine is without ergogenic effects during prolonged


55. Berglund, B., Hemmingson, P., Effects of caffeine ingestion on performance at low and


69. Doherty, M., The effects of caffeine on the maximal accumulated oxygen deficit and


APPENDIX A

Thesis Proposal
Title: The Effect of Ingesting Caffeine, Ephedrine, and their Combination on Repeated Strength Performance.

Principal Investigator: Mr. H. Pasternak

Co-Investigators: Dr. I. Jacobs, Mr. D.G. Bell

Background:

The search for safe and effective ergogenic (performance enhancing) aids has manifested itself in the arena of military operations. Due to the absence of doping tests and banned substances, the use of almost any effective and reasonably safe type of pharmacological or nutritional ergogenic aid is of interest to the military.

Caffeine is a well documented ergogenic aid. The ergogenic properties of caffeine have been attributed to the stimulation of the central nervous system and/or increased energy metabolism in the periphery via adenosine receptor blockade, improved neuromuscular transmission, increased muscle contractility, and increased catecholamine levels (Dodd et al, 1993). Many studies have established that caffeine on its own can prolong the time to exhaustion in prolonged continuous activity (Costill et al., 1978; Graham and Spriet 1991, 1995; Spriet et al., 1992; Trice and Haymes, 1995). In contrast, very few studies have examined brief intense exercise (90-100% VO2 max) after caffeine ingestion, and the results are unequivocal. Studies using isolated muscle have consistently shown caffeine to enhance muscle force production, while the majority of human studies have shown caffeine to have no effect on short term, high intensity performance. Studies (Bond et al. 1986; Williams et al. 1987, 1988) have shown that
Caffeine does not increase force, EMG activity, muscular endurance, or peak muscular force production during maximal voluntary (Bond et al. 1986) on involuntary (Lopes et al. 1983) electrical muscle stimulation. Most studies have also found that caffeine has no effect on short-term incremental exercise (Dodd et al. 1991; Gastin et al. 1990; Gaesser & Rich). However, studies from Flinn et al. (1990) and McNaughton et al. (1987) have shown efficacy with caffeine in graded incremental exercise. The lack of studies examining the effect of caffeine on sprint performance has left scientists wondering if caffeine has any effect on explosive type activities. Williams et al. (1988) reported that caffeine had no effect on maximal power output or muscular endurance during short, maximal bouts of cycling. Similarly, Collomp et al. (1991) found that ingestion of 5mg·kg of caffeine did not increase peak power or total work completed. Most studies agree that the extent of improvement appears to be dose related until a dose of 5-6 mg·kg\(^{-1}\), above which no further enhancement occurs (Graham and Spriet 1995; Passman et al. 1995).

Ephedrine is a sympathomimetic drug that is both an alpha and \(\beta\)-adrenergic agonist. It can stimulate adrenergic receptors in the CNS and the peripheral tissues via the displacement of norepinephrine from the nerve ending binding sites to the extracellular fluid (Gillman et al., 1990). Very little has been done in the way of acute ephedrine ingestion and exercise research. Before caffeine and ephedrine research at the DCIEM, the only two English studies that had been done with ephedrine and exercise (Sidney and Lefcoe 1977; Gillies et al. 1996) failed to show any ergogenic effect from ephedrine or pseudoephedrine on various exercise parameters. However, most of the data collected from our previous research would indicate that ephedrine, in combination with caffeine,
has definite ergogenic effects during exercise. Using 5mg·kg of caffeine and 1mg·kg of ephedrine, Belle et al. (1995, 1996) found no ergogenic effect during 45s anaerobic windgate tests or during maximum oxygen accumulated oxygen tests (MAOD). However further studies revealed the ergogenic efficacy of caffeine with ephedrine. Bell et al. (1997) found enhanced Canadian Warrior Test times (3.2 km run performed in “fighting order dress”) with the ingestion of 375mg of caffeine and 75mg of ephedrine. Furthermore, Bell et al. (1998a) found 5mg·kg of caffeine and 1mg·kg of ephedrine significantly prolonged cycle ergometer exercise time to exhaustion at 85% VO$_2$ max. Recent, unpublished data (Bell et al., 1998b), has found that the optimal ergogenic dose ratio for caffeine and ephedrine is 4.0mg·kg and 0.8mg·kg respectively. Regardless of the previous the studies mentioned, all showed that the ingestion of caffeine and ephedrine in combination (C+E) elicits a strong elevation in physiological and mental alertness, as well as increased blood sugars, FFA, glycerol, and catecholamines. Overall, the lack of studies with caffeine, ephedrine, and caffeine and ephedrine on strength has left many questions unanswered.

Purpose:

The purpose of this study to determine the acute effects of high dose caffeine and ephedrine ingestion on repetitive bouts of upper and lower body muscular strength.
Hypothesis:

It is hypothesized that the ingestion of caffeine and ephedrine will increase the total amount of weight lifted each set and overall. Therefore, caffeine and ephedrine will increase strength temporarily.

Methods:

Ten to fifteen male military and civilian volunteers, between 18 and 40 years of age, will be recruited from the DCIEM, the university community, and various Toronto area health clubs. Participation in the experiment will be subject to medical approval. Subjects will be informed fully of the details, discomforts, and risks associated with the experimental protocol and will have been granted medical approval before being asked for their written consent. The subject will be asked to refrain from heavy exercise for 24 hours before each session and to refrain from alcohol and caffeine for 12 hours before each session. Subjects will not be tested if they are taking any medication.

Experimental Protocol:

All subjects will undergo the following test protocol.

(a) **Session 1: **Medical screening and determination of one repetition maximum (1-RM) using smith machine bench press and 45 degree angle leg press. During the medical screening subjects will have electrocardiogram evaluation and a blood pressure check. Further, they will provide any information regarding history of heart disease, fainting, or dizziness. Prior to testing for the subject’s 1RM, 15 repetitions at half (bench press) or all (leg press) the subjects’ body weight will be performed as a warm up. To
estimate the subjects’ 1RM, they will perform their first press (bench and leg) at a
moderately heavy weight. Weight will continue to be added until the subject is unable to
perform one repetition.

(b) **Session 2**: A minimum of 1 week following session 1, the subjects will be
familiarized to the exercise protocol, i.e., the weight training circuit and the procedures
leading up to it. Before arriving at the laboratory they will have had a normal breakfast.
After arriving at the laboratory, a small (5 ml) sample of blood will be taken from the
cubital vein. Blood samples will later be analyzed for ephedrine, caffeine,
catecholamines, and -endorphins (Nehlig et al.1992). Following the blood analysis, the
subject will be asked to fill out a physiological state survey on how they are feeling. After
this, warm up for the weight training circuit (WTC) will commence. The warm up will
consist of the subject performing 30% of their 1RM of each of the exercises for two sets
of 15 repetitions each. The WTC consists of three supersets of one upper body exercise
(smith machine bench press) and one lower body exercise (leg press). Each set will be
done to concentric muscle failure at 85% of 1-RM. Subjects will raise and lower the
weights to the cadence of a metronome and will exercise to a 1:3 work to rest ratio
(Harre, 1992). The work effort is designed to have subjects reach concentric muscle
failure at approximately 8-10 repetitions. This session will last approximately 90 min.

(c) **Session 3**: A minimum of 1 week following session 2, each of the subjects will
participate in a second familiarization trial. This trial will be exactly like session two. It is
used to account for the learning effect that will occur from the second session and thus
give us a control run.
(d) Sessions 4-8: These will be the treatment trials. A minimum of 1 week following session 3, each subject will participate in 5 further trials performed on a weekly basis at the same time of the day. These trials will be identical to the familiarization sessions (trial 2 and 3), except that the subjects will ingest gelatin capsules containing either the drugs or placebo after the first blood sample. The subjects will also refrain from having breakfast, as a standardize meal (toast, juice, muffin) will be given 0.5 hours after drug ingestion. The combinations for the drugs are as follows: one trial will consist of 4mg·kg BW of caffeine; another will consist of 0.8mg/kg ephedrine; another will consist of 4mg·kg caffeine and 0.8mg·kg ephedrine (Bell et al, 1998b). There will also be two placebo trials. The placebo trials will have the subjects ingest the same amount of capsules as in the drug trials. The placebo capsules will contain a dietary fiber (Metamucil). Treatment trials will be randomized.

**Data Analyses:**

A one factor repeated-measures Analysis of Variance (ANOVA) will be used to compare the total work done (repetitions x resistance) for the treatment trials. When a significant effect is found (p < 0.05), a means comparison contrast technique will be employed to isolate differences among treatment means.

**Safety Recommendations and Risks:**

All subjects will be screened by a physician prior to the exercise trials.

The incidence of myocardial infarction in the general population has been estimated at about 1 in 10000 with maximal exercise tests (Gibbons et al. 1989). The risk
is even more remote considering the exercise performed in this study is more anaerobically based, thus, placing less stress on the heart. Furthermore, risk is also lessened due to the medical screening prior to the study. Emergency resuscitation equipment will be on hand at the locale and the investigators and technicians are trained and certified in cardiopulmonary resuscitation. Subjects may experience some stiffness in their legs, arms, and chest for one to two days after the experiment due to the intensity of the weight training.

There is a risk of nausea and vomiting when hard exercise is performed after ingesting caffeine and ephedrine. This risk should be reduced greatly due to the differences which exist between the weight training exercise used in this study and the more intense supramaximal cycle tests used in the previous studies which reported nausea and vomiting. Other side effects may include nervousness, insomnia, anxiety, and wakefulness. These side effects should dissipate within 24 hours. If any undue discomfort or side effects of ingestion are reported by the subject before or during exercise, the trial will be discontinued.

With intravenous catheterization, complications may include infection of the wound site and leaking of blood into the surrounding tissue (bruising). The possibilities exist, although extremely rare, that a broken piece of the apparatus or a bolus of air (in excess of 50 mL) could get into the circulation. Occasionally, fainting due to the nervous reflexes may occur during the catheterization. The catheter will be removed by the physician/technician following the end of the test with all precautions taken to prevent bruising at the wound site.


**Medical Officer Requirements:**

A medical officer will be required to perform the medical screenings before the experimental sessions begin. The presence of a medical officer in the exercise physiology laboratory will not be required during the actual experiment. His presence within the building is all that is necessary. All experiments will be conducted during regular working hours. Mr. Pasternak will inform the “covering” physician in advance of the experimental schedule, and will ensure that the medical officer is in the building before commencing these tests.

**Approximate Time Involvement:**

All sessions, with the exception of session #1, will require approximately 90 min. Due to the medical screening, session #1 will last closer to 2 hours.

**Extra Equipment Need:**

There will be a need for renting or borrowing the following equipment:

- 45 degree angle – plate loaded leg press.
- Barbell Smith Machine
- 20 -45 lb. plates
- 2 -25 lb. plates
- 2 -10 lb. Plates

The equipment requested above was chosen based on the following criteria:

- Safety
  - Very little need for technique training, therefore, less of a learning curve.
Remuneration of Subjects:

Subjects are entitled to a stress allowance for DND experiments as outlined in Memorandum 7200-2 (HPSD) December 1992.

Benefits of Study:

C+E has been demonstrated to be an effective ergogenic aid in exhaustive aerobic exercise. Furthermore, testimonial and anecdotal evidence suggests C+E may have a potent effect on strength training. However, there is an absence of research based evidence proving or disproving these claims. If the data collected in this study supports the efficacy of C+E on strength training, it may be a valuable tool for various military operations.

References (Thesis Proposal)


APPENDIX B
ETHICS COMMITTEE APPROVAL
University of Toronto

OFFICE OF RESEARCH SERVICES

PROTOCOL REFERENCE #4236

January 24, 2000

Dr. I. Jacobs
Chief Scientist
DCIEM
1133 Sheppard Ave. W.
PO Box 2000
North York, ON
M3M 3B9

Dear Dr. Jacobs:

Re: Your research protocol entitled “Effects of Ingesting Caffeine, Ephedrine, and C+E on Tests of Muscle Strength and Muscular Endurance” by Dr. I. Jacobs

We are writing to advise you that a Review Committee composed of Professors J. Goodman, J. Furedy, T. McLellan and Dr. R. Ogilvie has granted approval to this revised protocol.

The approved revised consent form (Nov. 15, 1999) is attached. Subjects should receive a copy of their consent form.

During the course of the research, any significant deviations from the approved protocol (that is, any deviation which would lead to an increase in risk or a decrease in benefit to human subjects) and/or any unanticipated developments within the research should be brought to the attention of the Office of Research Services.

Best wishes for the successful completion of your project.

Yours sincerely,

Benoit Morin
Ethical Review Officer

Cc: Prof. J. P. Landolt, Prof. M. Plyley
BM:mr
APPENDIX C
CONSENT FORMS
CONSENT FORMS

(1) Volunteer Consent Form

Project Title: The Effect of Ingesting Caffeine, Ephedrine, and their Combination on repeated strength performance.

Principal Investigator: Mr. H. Pasternak
Co-Investigators: Dr. I. Jacobs, Mr. D.G. Bell.

1. I, ________________________________________________________________
   (name, address, phone no.) hereby volunteer to participate as a test subject in the DCIEM experiment on the influence of caffeine and ephedrine ingestion on exercise performance (Protocol #L-197). I have had the opportunity to study and discuss the attached protocol with the investigator and physician and I have been informed to my satisfaction about the possible discomforts associated with these tests. I agree not to perform heavy physical exercise for 24 hours before each test and not to consume alcohol or caffeine for 12 hours before each test.

2. I am aware that my ten-repetition maximum will be measured by increasing the resistance on the bench press and leg press exercises until only ten repetitions can be completed.

3. I understand that there will be eight exercise sessions: a 10-RM session, 2 familiarization sessions to the weight training circuit, and 5 treatment sessions. I am aware that all weight training sets will go to exhaustion.

4. I understand that a needle will be inserted to my cubital vein and a sample of blood will be taken prior to each of the sessions.

5. I have been told that the principal risks of this experiment involves emesis or vomiting associated with drug ingestion and exercise. I understand and accept these risks. I have also been informed about remote myocardial infarction risk and possible muscle tear/pull associated with this study and consider this risk acceptable. In addition, I understand that this experiment may involve risks that are presently unforeseen and that I may be exposed to these risks. I accept this possibility.

6. I hereby consent to the medical screening assessment outlined in the protocol and agree to provide responses to questions that are to the best of my knowledge truthful and complete. Furthermore, I agree to advise the investigators of any health status...
changes since my initial assessment (including but not limited to viral illnesses, new prescription or 'over-the-counter' medications, or any other drug ingestion). I have been advised that the medical information I reveal and the experimental data concerning me will be treated as confidential and not revealed to anyone other than the investigators without my consent except as data unidentified as to source. I am aware that a physician will be on-call in DCIEM during all sessions.

7. I am aware that I must not donate blood within 30 days of any part of this experiment. I am also aware of the requirement to sign a separate consent form for invasive medical procedures. In the highly unlikely event that I become incapacitated during my participation, I hereby consent to whatever emergency medical intervention deemed necessary by the attending medical personnel. I also agree that I will go with the investigator to seek emergency medical attention if either I or the investigator considers that it is required.

8. I acknowledge that I read this form and I understand that my consent is voluntary and has been given under circumstances in which I can exercise free power of choice. I have been informed that I may, at any time, revoke my consent and withdraw from the experiment, and that the investigators or the physician may terminate my involvement in the experiment, regardless of my wishes.

Signature

Print Name

Witness Date

Subject fit to participate as assessed by Physician

For military personnel on permanent strength at CFEME:
Approval in principle by Commanding Officer is given in Memorandum 3700-1 (CO CFME), 18 Aug 94; however, members must still obtain their Sector head's signature designating approval to participate in this particular experiment. CF personnel are considered to be on duty for disciplinary, administrative and Pension Act purposes during their participation in this experiment.

For other military personnel:
All other military personnel must obtain their Commanding Officer's signature designating approval to participate in this experiment.

For civilian personnel at DCIEM:
Signature of your Sector Head is required designating approval to participate in this experiment.
Sector Head's/Commanding Officer's Signature:
CO's Unit Principal Investigator

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(2) INVASIVE PROCEDURES CONSENT FORM

Project Title: The effect of acute caffeine+ephedrine ingestion on upper and lower body strength.
Principle Investigator: Mr. H. Pasternak
Co-Investigators: Dr. I. Jacobs, Mr. D.G. Bell

1. Venous Blood Sampling: A small needle is used to pierce the skin overlying a vein. This venipuncture is used to obtain a blood sample prior to exercise, as detailed in the subject information package. Either a physician or a properly qualified and physician-authorized technician performs the venipuncture. Complications may include infection of the wound site and leaking of blood into the surrounding tissue (bruising). Occasionally, fainting due to nervous reflexes may occur during the venipuncture.

Subject’s Declaration:

I (print name)__________________________ hereby consent to the procedures that I have initialed above. The procedures and their complications have been explained to me to my satisfaction by the investigator(s). In addition, I have had the opportunity to ask questions both of the investigator(s) and of a physician.

Subject:_________________________ Date:____________________
signature

Witness:_________________________ Date:____________________
signature
APPENDIX D
ASSAY PROCEDURES
ASSAY PROCEDURES

(1) Caffeine and Ephedrine Assays

Samples:
- The construction of a worksheet which assigned codes to each subject
- Two sets of tubes for each sample were labeled and pipetted with 200ul of plasma
- The addition of 100ul of ephedrine internal standards and 200ul of caffeine internal standard.

Standards:
- Preparation of stock aqueous ephedrine standards by weighing out 12.20 mg of HCl dissolving in 10 ml·s⁻¹ to get a 1000ng·ul⁻¹ stock.
- Preparation of aqueous caffeine working standards of 1 ng·mL⁻¹, 10ng·uL⁻¹, and 100ng·ul.
- Preparation of aqueous working ephedrine standards of 0.1 and 1 ng·uL⁻¹.
- Preparation of a standard curve for ephedrine of 10, 20, 50, and 100 ng·tube⁻¹.
- Preparation of a standard curve for caffeine of 100, 500, 1000, and 5000 ng·tube⁻¹.

Internal Standards:
- Preparation of an aqueous working caffeine standard of 0.5 ng·ul⁻¹ by adding 125 uL of 100ng·uL⁻¹ stock to 25 ml volumetric flask. After the addition of 100 ul of 0.1% sulphite,
water was added to the 25 ml mark. The final concentration is 100ng·tube⁻¹ of caffeine internal standard.

-Preparation of aqueous working ephedrine standard of 0.5 ng·ul by adding 125 ul of 100ng·uL⁻¹ stock in freezer to a 25 ml volumetric flask. The addition of 100 uL of 0.1% sulphite was followed by the addition of water the 25 ml mark.

**Standard Curves:**

- The addition of 100 ul of ephedrine internal standard and 200 ul of caffeine internal standard to each screw cap tube (one per sample)
- The addition of 100ul of potassium carbonate, 500ul of H₂O and 1 ml of toluene were rotorackted for 20 min.
- The tubes were then centrifuged for 5 min at 3000rpm, and the top layer of toluene was transferred to second tubes
- This toluene extraction was performed three times
- After the third extraction, the second tubes, to which the toluene had been transferred, was blown down using nitrogen at 40 degrees until just a small drop remained.
- The addition of 100 µl of P.F.P.A. (pentfluoropropionic anhydride) was added to the blown down samples and was then heated for 30 min at 60 degrees.
- Samples were then blown down again under nitrogen until just dry and 500 µl of toluene were added.
- Samples were then transferred into mass spectrometry tubes and placed into the mass spectrometry machine, which was set at 15m DBXLB.
(2) Plasma β-Endorphin Assays.

To assay for β-endorphin, 5 mL venous blood samples were collected in pre-chilled, evacuated glass vacutainers (Becton Dickinson, Oakville, ON) containing tripotassium ethylenediamine tetra-acetate (K₂EDTA, 7.2 mg · 5 mL⁻¹ blood). The tubes were immediately placed on ice for transport to the centrifuge and centrifuged at low speed (760 x g; 1700 RPM) for 15 min at 4°C. The plasma layer was collected with 2 mL disposable plastic pipettes and transferred to individual, frozen, sterile polypropylene Eppendorf tubes. All samples were stored at -70°C until assayed in duplicate.

Plasma samples (1 mL) were assayed for β-endorphin, using an affinity gel-extraction and radioimmunoassay procedure (INCSTAR, Stillwater, MN). The assay was performed according to the manufacturer's instructions. The first step in this method involved the extraction of β-endorphin from plasma using specific adsorption particles (Sepharose particles). Briefly, 0.5 mL of well-mixed rabbit, anti-β-endorphin coupled Sepharose particles were added to each chromatography column containing 1 mL of sample or standard. Following 4 h of column rotation (end over end) at 4°C, the plasma was allowed to drain through the column. The adsorbed β-endorphin was quickly eluted from the particles using 250 μL of 0.025 N HCL (x2). The eluted β-endorphin was assayed in duplicate using a sensitive ¹²⁵I-RIA (with this method, cross-reactivity with -lipotropin, [Leu]- and [Met]-enkephalins, and ACTH is less than 0.01%). All of the samples from an individual were analyzed in the same assay to avoid errors due to inter-assay variability.
APPENDIX E
SUBJECT RECRUITMENT POSTER
Volunteers Wanted For Exercise Study

Purpose: • To evaluate the effect of Caffeine, Ephedrine, and their Combination on repeated strength performance

When: • starts Nov 98

Where: • Exercise Physiology Laboratory
     Environmental Physiology Section
     DCIEM at CFB Toronto
     Corner of Sheppard Ave. W. and Allen Expwy

Time Required: • approximately 1/2 day per test day
     • 9 sessions over an 8-week period

Tests: • upper and lower body strength
     • Blood sampling

Feedback to You: • Evaluation of your muscular endurance in a reputable and state-of-the-art exercise laboratory

Prerequisites: • Healthy Males, 18 - 40 years
     • Familiar with exhaustive exercise
     • No history of heart disease, high blood pressure, dizziness or fainting spells

Payment: • Participants will receive a stress allowance

Contact • Mr. Harley Pasternak 416-635-3098
     • Dr. Ira Jacobs 416-635-2123
APPENDIX F
ONE-REPETITION MAXIMUM CHART
Table 26.1  Estimating One-Repetition Maximum

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APPENDIX H
EXERCISE EQUIPMENT PHOTOGRAPHS