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Caffeine and performance in altitude

Endurance performance in acute hypoxia following 4 mg • kg⁻¹ caffeine ingestion

Master thesis in Sport Sciences
Department of Physical Performance
Norwegian School of Sport Sciences, 2014

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Thanks

This is it; this marks the end of some amazing years at The Norwegian School of Sport Sciences. I have learned a lot on the journey towards a master thesis. Today I am very happy and proud to have finished.

A lot of people deserve special thanks for their contribution the last years. My supervisor *Jørgen Jensen* is just amazing. You are always available when I need to discuss something. Regardless if the subject is physiology or wine you are more than happy to spare some minutes on me. I have really enjoyed every discussion. Secondly my greetings go to my secondary supervisor *Hans Kristian Stadheim*. You are always in a good mood and helpful regardless of the time of the day. Your charisma and eager for knowledge transmits to all around you. I would also like to thank my family, and specially my lovely fiancée and study-colleague *Melina Meyer Magulas* for all the support during this process. *Kristoffer Bergstrøm* and *Even Granerud* at the office deserve thanks for making the long days and nights livable.

Other people that have been involved and deserve special thanks are: *Matt Spencer*, *Trine Stensrud*, *Astrid Bolling*, *Svein Leirstein*, *Raymond Olsen* and last but not least; the test subjects! You might not be as good as me in card-games, but you guys are amazing!

Eirik Myhr Nossun

Oslo, 2014

Summary

Introduction: Various studies have observed improved endurance performance (EP) following caffeine ingestion (CAF) at lowland. However, the effects CAF have on an endurance performance in altitude have so far been given little scientific interest. This master thesis was therefore designed to study the effects of CAF on an 8 km cross-country poling performance test (8 km C-PT) during acute exposure to altitude (2000 meters above sea-level). Physiological measurements during a submaximal incremental test prior to the 8 km C-PT were conducted to understand possible mechanisms behind an eventually improved performance.

Method: The study had a randomized, double-blinded, cross-over design. 9 highly trained cross-country skiers fulfilled the inclusion criteria's. All test subjects underwent familiarization training prior to the main tests on a cross-country poling ergometer (CC-POL). One 8 km C-PT was performed in lowland and two 8 km C-PT was conducted in altitude. Half of the TS were given CAF ($4 \text{ mg} \cdot \text{kg}^{-1}$) the first 8 km C-PT in altitude and the other half received placebo (PLA). Logically TS were given opposite treatment on the second and last 8 km C-PT. Before each 8 km C-PT TS performed a submaximal incremental test of four 5-minute workloads. Exercise intensity was 55-70 % of the individual $\text{VO}_{2\text{max-altitude}}$.

Results: Results show a small but possible enhancing effect on the time to complete the 8 km C-PT following caffeine ingestion compared to placebo. Average time used in altitude was 32.36 ± 2.24 minutes after caffeine ingestions and 32.78 ± 2.45 after placebo. The enhanced performance was mainly due to a higher velocity the first 3 km of the test. Time used on the 8 km C-PT at lowland was 30.99 ± 3.32 minutes. Lactate concentrations were significantly increased both during the incremental test and after the 8 km C-PT in altitude following caffeine ingestion. Heart rate was significantly increased and blood bicarbonate significantly decreased following caffeine ingestions during the 8 km C-PT. In addition, no difference in muscular pain was observed during the performance-test, but subject reported lower perception of pain in the arms after three of the four submaximal workloads.

Conclusion:

Caffeine ingestion showed a possible enhancing effect on time to complete the 8 km C-PT. The increased HR seen during the 8 km C-PT would indicate that TS was able to work harder following caffeine ingestion compared to placebo. Although no differences in RPE was reported one might imagine caffeine, due to the increased workload, actually lowers RPE.

Keywords:

CAFFEINE, ALTITUDE, LACTATE, HR, RPE, PAIN, BICARBONATE

1.0 Introduction

Researchers have the last 40 years studied caffeine in order to investigate its potential to improve an endurance performance (EP). These studies have shown a small but convincingly enhancing effect on performance following caffeine ingestion. Most of the endurance protocols used to investigate this effects vary between 30-120 minutes and the subjects are given orally $3 \text{ mg} \cdot \text{kg}^{-1}$ to $9 \text{ mg} \cdot \text{kg}^{-1}$ caffeine 40-60 minutes prior to the endurance task (Goldstein et al., 2010).

Although many studies have observed enhanced performance after caffeine ingestion, the mechanisms underlying the ergogenic improvements are so far unclear, and seem complex. One theory is caffeine's ability to influence human metabolism and utilize fat, and so on spare glycogen (Essig, Costill, & Vanhandel, 1980). This theory suggests that during exercise one would utilize relatively more fat at the same relative workload after caffeine ingestions compared to placebo. Many newer studies fail to find this change in metabolism (Graham, 2001; Stadheim, Kvamme, Olsen, Drevon, Ivy & Jensen, 2013). Caffeine has the ability to bind at adenosine receptors. A second theory states that by binding to these receptors, caffeine might affect the central nervous system by reducing the perception of pain and increasing the heart rate (HR) (Fredholm, Battig, Holmen, Nehlig, Zvartau, 1999).

As altitude increases, the atmospheric pressure decreases. The partial pressure of oxygen reduces, and to compensate the human body increases the HR and starts to breathe faster. Trained athletes often have a lowered hypoxic ventilatory response (HVR) compared to untrained (Durand, Mucci & Prèfaut, 2000). Competitions in altitude (1500 – 2000 meters above sea-level) are common in many endurance sports. To prepare for these competitions athletes often choose one of two approaches. They either train in altitude for several weeks before the competition (chronic hypoxia), or they stay at lowland right until the competition (acute hypoxia).

In the world-cup of cross-country skiing (2012-2014) there were 9 competitions in altitude (≥ 1500 meters above sea-level). In addition, the cross-country stadium at the winter Olympic Games 2014 was at 1500 meters above sea-level. The use of caffeine in sports is mainly due to its performance enhancing effects (Burke, 2008). For this reason many Norwegian cross-country skiers use caffeine ingestion prior to competitions.

However, it is not well documented that caffeine ingestion improves performance at altitude. Hemminsson & Berglund (1982) and Fulco

2.0 Research aim

The main aim of the study was to investigate the effect of $4 \text{ mg} \cdot \text{kg}^{-1}$ caffeine on an 8 km C-PT in altitude (2000 meters above sea-level), where upper body and arms limits the EP. Furthermore the study aimed to investigate how physiological parameters such as lactate, glucose and bicarbonate are affected by caffeine in the same altitude.

Additionally we wanted to examine how subjective parameters such as muscular pain and rate of perceived exertion (RPE) were influenced following caffeine ingestion in altitude.

2.1 Hypothesis

We hypothesized caffeine ingestion would improve an endurance performance in altitude as previous observed in lowland.

3.0 Theory

3.1 Caffeine – history and chemistry

Caffeine ($C_8H_{10}N_4O_2$), or 1,3,7-trimethylxanthine, belongs to a family of compounds known as methylxanthines (Graham, Rush & Van Soeren, 1994). The hydrophobic properties of the caffeine-molecules allow passage through all biological membranes in humans, including the blood-brain barrier (Tanaka, Nakazawa, Arima & Iwasaki, 1984). Caffeine has the ability to block adenosine receptors throughout the whole human body if ingested in sufficient amounts (table 3.1).

Table 3.1: Potency of caffeine in rat and human adenosine receptor subtypes.

Receptor subtype	Rat (K_D)	Human (K_D)
		μM
A ₁ receptors	20	12
A _{2A} receptors	8.1	2.4
A _{2B} receptors	17	13
A ₃ receptors	190	80

Note. Table 3.1 is obtained from: Fredholm et al., (1999). *Pharmacological review*, 51, 83-133.

Caffeine is today the worlds most consumed drug due to the many different beverages and foods in which caffeine is an added compound (Tarnopolsky, 1994; Davies & Green, 2009). There is mythological evidence regarding usage of caffeine back to the 8th century, although there is a lack of solid scientific evidence. The first evidence that proves consumption of coffee originates in the sixteenth century when coffee houses started to develop in the Muslim part of the world (Fredholm, 2011)

When caffeine is absorbed from the gastrointestinal tract, peak plasma caffeine concentrations are reached after 15-60 minutes (table 3.2). Regarding to this, most studies have given caffeine ingestion 45-60 minutes before their respective EP-test. Caffeine concentrations will vary, both in plasma and in urine, with the amount ingested and the amount of liquid in the body (Fredholm et al., 1999). Normal dosage of orally given caffeine in scientific studies vary between $3 \text{ mg} \cdot \text{kg}^{-1}$ and $9 \text{ mg} \cdot \text{kg}^{-1}$. Table 3.2

shows how different dosages of caffeine ingestion would affect both urine and plasma concentrations of caffeine.

Table 3.2: Approximately urine and plasma values of caffeine after different caffeine intake

Dosage of caffeine	Urine concentration ($\mu\text{mol} \cdot \text{l}^{-1}$)	Plasma concentration ($\mu\text{mol} \cdot \text{l}^{-1}$)
2 mg \cdot kg ⁻¹	0.5 – 3.0	5 – 10
3 mg \cdot kg ⁻¹	1.5 – 3.5	10 – 20
4 mg \cdot kg ⁻¹	1.5 – 4.5	15 – 30
5 mg \cdot kg ⁻¹	2.0 – 5.5	20 – 50
6 mg \cdot kg ⁻¹	3.0 – 8.0	30 – 50
9 mg \cdot kg ⁻¹	6.0 – 11.0	40 – 80

Data is obtained from: Stadheim et al., (2013)

3.2 Caffeine and performance

Studies involving caffeine ingestions prior to endurance exercise have shown improved performance when tested in work output or time to exhaustion (Goldstein et al., 2010; Fredholm et al., 1999; Ormsbree, Bach & Baur, 2014; Sökmen, Armstrong, Kraemer, Casa, Diaz, Judelson & Maresh, 2008). During short term exercise (less than 5 minutes) there are divergent results of the effects caffeine ingestions have on performance.

Ormsbree et al., (2014) suggest this is because of the limited studies on the topic or that caffeine may have no effect on short performance tasks. During prolonged exercise (time \geq 10 minutes) there are numerous studies showing enhanced performance after orally given caffeine ingestions (3 mg \cdot kg⁻¹ to 9 mg \cdot kg⁻¹) (Stadheim, Spencer, Olsen & Jensen, 2014; Stadheim et al., 2013; Irwin, Desbrow, Ellis, O’Keeffe, Grant & Leveritt 2011; Dean, Braakhuis & Paton, 2009; Ivy, Kammer, Ding, Wang, Bernard, Liao & Hwang, 2009).

Cycling and running are the most frequent method used to measure performance following caffeine ingestion, but cross-country skiing and rowing are also occasionally used. Of the studies conducted on endurance performance duration and methods vary. Time trials (TT) (Dean et al., 2009; Stadheim et al., 2013; Stadheim et al., 2014), time to exhaustion (TTE) (Ping, Keong & Bandyopadhyay, 2010) and shortest possible time use on a fixed amount of work (Ormsbree et al., 2014) are all common methods used to test effects of caffeine ingestion. Duration of EP between 30 and 120 minutes after

orally given caffeine ingestion are most common. The orally given caffeine is in most cases given as tablets or in powder form dissolved in liquid and added flavor to cover taste. Some studies also use common caffeinated liquids such as Red Bull (Ivy et al., 2009).

3.2.1 Cross-country skiing

Cross-country is common as a sport in many northern countries. Classical technique is used more compared to skating technique. Double-poling (DP) is one of the under-techniques used in relatively flat terrain. During DP the upper body is mainly used and arms produce the force to gain speed. Hence, the muscles of the upper body are the limiting factor of performance (Stadheim et al., 2011). One of the most important long distance races, Vasaloppet, was actually won using only DP technique in 2013 by Jørgen Aukland. Studies show that substrate utilization and the ability to extract oxygen is lower in the muscles of the upper body compared to leg muscles (Calbet, Holmberg, Rosdahl, Van, Jensen-Urstad & Saltin, 2005; Helge, 2010; Van Hall, Jensen-Urstad, Rosdahl, Holmberg, Saltin & Calbet, 2003). The same authors also reports of higher blood lactate and carbohydrate utilization in upper body exercise compared to leg exercise at the same relative workloads.

Cross-country is an endurance sport with competition usually lasting from 4 min – 2 hours. Caffeine usage among endurance athletes is widespread (Stadheim et al., 2013; Goldstein et al., 2010). Despite this, few authors have studied the effect of caffeine upon an endurance performance (EP) in cross-country skiing. The last 5 years upper body strength has increased among cross-country athletes, DP technique has become more used (Trond Nystad, chief of the Norwegian Cross-country team, personal communication, 1. januar, 2014). Both Stadheim et al., (2013) and Stadheim et al., (2014) reported interestingly an enhanced DP performance after caffeine ingestion.

3.3 Caffeine and mechanisms / theory of action

3.3.1 Glycogen sparing theory

Caffeine ingestion has been proposed to result in an enhanced fat oxidation due to adrenaline secretion in the blood stream (Costill, Dalsky & Fink, 1978). An enhanced fat oxidation during physical activity may be beneficial due to a sparing of the glycogen stored in the muscles. In EP having a relatively long duration (> 80 min),

glycogen depletion might negatively affect the performance. In this long lasting submaximal EP, sparing of the glycogen might therefore result in an enhanced EP. In Costill et al., (1978), 9 highly trained cyclists, exercised at 80 % of VO_{2max} until exhaustion. Coffee (330 mg) significantly increased time to exhaustion compared to decaffeinated coffee. Increased fat oxidation was observed following caffeine ingestion, and the authors suggested the enhanced performance was due to this greater rate of lipid metabolism, and a sparing of glycogen storages. While some authors (Costill et al., 1978; Essig et al., 1980) show data to support the theory with increased FFA, others fail to show increased FFA oxidation after caffeine ingestion both during and after an endurance performance (EP) (Tarnopolsky, Atkinson, MacDougall, Sale & Sutton, 1989; Erickson, Schwarzkoff & McKenzie 1989).

3.3.2 Caffeine and CNS

Impact on the central nervous system (CNS) has been purposed as a way of explaining the enhanced EP after caffeine ingestion (Graham, 2001; Goldstein, 2010). The suggested action of caffeine on CNS is multifunctional, thus acts both on peripheral and central neurons. Caffeine can either bind directly to receptors on the cell surface, increasing the release of neurotransmitters or inhibit the reuptake of neurotransmitters (Magkos & Kavouras, 2004). Adenosine works among other as a neurotransmitter in the CNS. Caffeine has the ability to bind to adenosine receptors, and thereby prevent adenosine of acting on the CNS. Additionally, if neurotransmitters are inhibited from reuptake, they will be able to activate receptors by binding to them. Caffeine may inter alia influence motor unit recruitment and affect the perception of fatigue and pain. Additionally caffeine affects other physiological factors which direct or indirect might influence an EP.

The sympathetic nervous system regulates several physiological responses, including heart rate (HR), respiratory rate and substrate utilization. Specially two catecholamines, epinephrine and norepinephrine, mediate the sympathetic nervous system. Niess et al. (2003) showed increased in plasma epinephrine and norepinephrine after a high-intensity session done in moderate altitude (1800 m) compared to the same session at sea level.

3.3.3 Caffeine, Pain and Rating of Perceived Exertion (RPE)

Several studies suggest the enhanced performance observed after caffeine ingestion might result from a decreased perception of muscular pain and / or lower rating of perceived exertion (RPE) (Costill et al., 1978; Doherty & Smith, 2005; Bell, Jacobs & Zamecnik, 1998; Casal & Leon, 1985; Bell & McLellan, 2002).

Rating of Perceived Exertion (RPE) are often used to measure how a subject sense the intensity of exercise or competition. The intensity is measured using Borg's scale (Borg, 1998), ranging from 6-20 where 20 means "maximal exertion" and 6 means "no exertion at all". Doherty & Smith (2005) examined how caffeine affected RPE during submaximal workloads in their meta-analysis. They report a 6 % reduction in RPE during constant submaximal workloads following caffeine ingestion compared to placebo. Irwin et al. (2011) examined caffeine ingestion on twelve male cyclists who were all coffee-drinkers. They conducted a TT with two different dosages of caffeine or placebo. During the incremental test caffeine lowered RPE. During the TT the differences was not seen. This was not surprising because the subjects were pushing maximal during the TT. Stadheim et al., (2013) reported no differences in RPE during a 8 km C-PT DP after caffeine ingestion compared to placebo. However, during a submaximal incremental test, RPE was lowered following caffeine ingestion at intensities of 60-70% of VO_{2max} . Stadheim et al., (2014) reported a tendency of lowered RPE during a submaximal incremental test after ingestion of both $3 \text{ mg} \cdot \text{kg}^{-1}$ and $4.5 \text{ mg} \cdot \text{kg}^{-1}$ caffeine compared to placebo ($p < 0.1$). No differences in RPE were reported after a 10 min all-out DP test between the two different caffeine concentrations and placebo.

The effect caffeine has on the perception of pain is most documented in studies conducted on patients with different traumas. In humans there is observed reduction in pain such as headaches (Sawynok, 2011), neck pain and patient with intermittent tetraplegia, after ingestion with caffeine. An increased tolerance of pain is likely to result in an enhanced endurance performance. Momsen, Jensen, Norager, Madsen, Vestersgaard-Andersen & Lindholdt, (2010) showed that 88 patients with intermittent claudication enhanced their ability to walk on a treadmill-test by 20.5% after caffeine

ingestion. It was suggested that this was a result of a lowered pain at the start of the test. During the 8 km C-PT DP in the study by Stadheim et al., (2013) TS enhanced their performance following caffeine ingestion, but no differences in perception of muscular pain in either arms or legs was observed compared to placebo. However, a significantly higher pain was reported in the arms compared to the legs. As the arms generate the force to gain speed in DP-technique these differences in pain between arms and legs are easy to imagine.

3.4 Altitude

The interest in exercise and performance at altitude and altitude training can be traced back to the Olympic Games taking place in Mexico City 1968. At an elevation of 2300 m, sprinters and jumpers set several world records, but long distance runners ran markedly slower than the world records. Athletes born and raised in high altitude did relatively well compared to earlier races (Wilber, 2004). Today there is an upper altitude limit of 1800m in cross-country skiing competitions. Even at this altitude many of the Norwegian cross-country skiers report of reduced endurance capacity and an increased risk of fatigue due to speed shifts during a competition (Trond Nystad).

As altitude increases, there is a decrease in the partial pressure of O₂ in the air (PIO₂). This condition, termed hypoxia, leads to lower oxygen deficiency in arterial blood and muscle, a condition called hypoxemia (Wehrlin & Hallèn, 2006). The response to hypoxia is classified by its degree and period of exposure. Wehrlin & Hallèn (2006) classify two types of hypoxia; the acute (minutes to hours) and the chronic (days to years).

As the altitude increases, both the maximal oxygen uptake (VO_{2max-altitude}) and the aerobic performance decrease (Fulco, Rock & Cymerman 1998; Wehrlin & Hallèn, 2006). The decline in VO_{2max} is known to be a response to a reduced inspired oxygen tension (PIO₂) (Gavin, Derchak & Stager, 1998; Martin & O’Kroy, 1993). Highly trained endurance athletes show a larger decline in VO_{2max} with increasing altitude compared with untrained individuals (Gavin et al., 1998; Wehrlin & Hallèn, 2006). The study from Wherlin & Hallèn (2006) indicates that VO_{2max} decreases with 4.6 – 7.5% per 1000 meters of altitude.

Hemmingson & Berglund (1982) studied how caffeine ingestion ($6 \text{ mg} \cdot \text{kg}^{-1}$) influenced a 21 km cross-country skiing performance both at lowland and at 2.900 meters above sea-level. The performance-test in altitude was conducted after 3 days of acclimatization. Caffeine ingestion significantly reduced the time to complete the 21 km in altitude by 3.18 % corresponding 152 seconds ($p < 0.01$). At lowland caffeine ingestion tended to enhance performance ($p < 0.1$) but not with more than 1.7 % corresponding 59 seconds. They did not observe any differences in RPE during the 21 km in either lowland or altitude between caffeine and placebo.

Fulco, Rock, Trad, Rose, Forte, Young & Cymerman (1994) examined how time to exhaustion in cycling at 80 % of $\text{VO}_{2\text{max}}$ was influenced following $4 \text{ mg} \cdot \text{kg}^{-1}$ caffeine ingestion in altitude. They conducted the study at sea-level, during acute hypoxia, and during chronic hypoxia. Both of the altitude-tests were performed at 4.300 meters above sea-level. No differences in time to exhaustion were observed at sea-level between caffeine or placebo treatment. During acute hypoxia, caffeine enhanced the time to exhaustion with remarkable 54% (22.77 to 35.10 min, $p < 0.01$) compared to placebo. After 2 weeks of acclimatization to altitude, caffeine tended to improve the performance (24 %), however not with the same amount of time as during acute hypoxia (30.52 to 38.63 min, $p < 0.1$). They did not measure any physiological data which could explain the incredible enhancement in performance. They however concluded that a lessening of an altitude-induced impairment of muscular force following caffeine ingestion would explain the improvement in submaximal exercise performance in acute altitude.

3.4.1 Acute hypoxia

One of the initial physiological responses to acute exposure to altitude is an increase in pulmonary ventilation (V_E) in order to provide tissues and organs with sufficient oxygen (Wilber, 2004). Peripheral chemoreceptors sense hypoxic changes and sends signals through the nervous system to the ventilatory control center in the brain, in which increases V_E within minutes of exposure to hypoxia. Several studies have shown increased hypoxic ventilatory response (HVR) both during intermittent acute hypoxic exposure (Garcia, Hopkins & Powell, 2000), and during natural altitude acclimatization (Rivera-Ch, Gamboa, Leon-Valverde, Palacios, O'Connor & Robbins, 2003; Sato, Severinghaus & Bickler 1994).

An increased HVR causes a decrease in arterial PCO_2 . The majority of CO_2 transported to the lungs and expired by ventilation. Bicarbonate (HCO_3^-) and H^+ react to carbonic acid (H_2CO_3) in the capillaries (Åstrand, 2003). This will increase the pH of the blood, because HCO_3^- is reduced, and stimulate the kidneys to increase the production of more HCO_3^- (Guyton & Hall, 2011). By time this will bring pH back to its normal values. After 3 weeks of living in altitude, Gore et al., (2001) observed an increase in HCO_3^- concentrations, and therefore an increased buffering-capacity.

At the same relative submaximal workload, the hearts minute volume (MV) increases to compensate the decreased partial pressure of oxygen in altitude. Because stroke volume (SV) is unaffected / marginally affected, this happens by increasing heart rate (HR) (Mazzeo, 2008). Stimulation of the sympathetic nervous system and increased amounts of circulating epinephrine is two of the reasons why HR increases when exposed to acute altitude (Mazzeo, 2008). Additionally a withdrawal of parasympathetic activity is observed, and may also partially result in the increased HR seen in altitude (Hughson, Yamamoto, McCullough, Sutton & Reeves, 1985).

3.5 Lactate

Lactate is continuously produced in the human body both at rest and during exercise. As glucose is broken down to pyruvate in the glycolysis, lactate is formed when the accessibility of O_2 is insufficient. During strenuous exercise lactate-removing tissue is not able to remove lactate from the blood in the same speed as it is produced, thus lactate concentrations rise. High blood lactate levels with accompanying high concentrations of H^+ are known to promote skeletal muscle fatigue. High concentrations of H^+ may impair with the actin-myosin cross-bridge cycling, reduce troponin's sensitivity for calcium (Ca^{2+}) and reduce ATP-production by inhibiting the enzyme phosphofructokinase (PFK) (Dahl, 2008).

After caffeine ingestion, studies have observed increased concentrations of lactate both during rest and after exercise (Davis & Green, 2009; Stadheim H K., 2013; McNaughton, Siegler & Midgley, 2008; Graham, 2001). The increased concentrations observed after exercise are suggested to follow increased levels of adrenaline or an increased ability to push harder after caffeine ingestion (Davis & Green, 2009). Increased levels of adrenaline would potentially increase performance and lactate

concentrations via an increased glycolytic flux (Tarnopolsky et al., 1989). The ability to push harder would potentially increase lactate concentrations due to the fact that one might hold the intensity for a longer period of time or conduct a task at a higher intensity (Davis & Green, 2009). The lowered perception of pain are likely one of the factors contributing to the ability to push harder.

The response in blood lactate to rest and exercise at altitude has been widely discussed, and has been referred to as a “lactate paradox”. Some authors suggest hypoxia causes an increased response in lactate production in both submaximal and maximal exercise (Reeves, Wolfel, Green, Mazzeo, Young, Sutton & Brooks, 1992). Other authors suggest on the contrary that the response to hypoxia is decreased response in lactate production due to hypoxia (McLellan, Jacobs & Lewis, 1988). Common to most studies on the topic are the relatively high altitude (> 2000 meters) in which the studies are conducted. The test subjects are also often lowlanders acclimated to altitude or native high-landers (Hochachka, Beatty, Burelle, Trump, McKenzie & Matheson, 2002). However, this acute response is not seen after acclimation to altitude (Van Hall, Calbet, Søndergaard & Saltin, 2001).

3.6 Bicarbonate

In the resting human being, arterial blood pH is approximately 7.4, thus slightly alkalotic. Every applied stress (i.e. eating, exercise, altitude) will interplay with the systems which are regulating the blood pH towards normal, and those who move pH away from normal. In the human body, the ability to maintain homeostasis between formation and removal of hydrogen ions (H^+) is crucial. One of the mechanisms for adjusting and regulating acid-base balance in the human body is the excretion of H^+ through pulmonary ventilation (McNaughton et al., 2008).



During strenuous exercise, the cell metabolism produces lactate (lactic acid). A proton is liberated, which binds with bicarbonate and forms lactate and carbonic acid. This, in time, forms water and carbon dioxide, and CO_2 is removed from the body by expiration (McNaughton et al., 2008).

The cells in the human body generate and excrete large quantities of carbon dioxide (CO_2) during aerobic metabolism of glucose and fat. As much as 70-75 % of all

CO₂ in the body is converted into carbonic acid (H₂CO₃), in which quickly is turned into bicarbonate (HCO₃⁻). Thus, the body is independent of ingestion of exogenous compounds to maintain this buffering system.

Via breathing, the bicarbonate system is in equilibrium with the external environment. Thus it is able to respond rapidly to endogenous alterations. The acid components of bicarbonate (H⁺ and CO₂) are independent of complex transport kinetics because they can cross biological membranes rapidly. The base component (HCO₃⁻) depends on anion exchange, to be transported into cells.

Hypoxic ventilatory response (HVR) is one of the initial responses as altitude increases and oxygen pressure decreases. As more CO₂ is expired by increased ventilation the concentration of HCO₃⁻ will decrease. The equilibrium shifts caused by expired CO₂ will reduce HCO₃⁻, and the buffer capacity in plasma for H⁺ is lowered. Caffeine increases ventilation similarly as hypoxia (Chapman & Mickleborough, 2009). No studies as far as the author know have studied the effects the combination of altitude and caffeine ingestion has upon the bicarbonate-buffering system

4.0 Methods

Test subjects (TS) were recruited from a local cross-country skiing club, and at the Norwegian School of Sports Sciences (NSSS). All was either competitive athletes, or was students at a high competitive level in the same sport. Inclusion criteria's:

- I. TS had participated in the Norwegian cross-country / biathlon skiing cup within the last three years.
- II. TS were highly trained male, with VO_{2max} above $65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in a standardized VO_{2max} running test.
- III. TS did not have claustrophobia.
- IV. No known heart diseases

Table 4.1: Anthropometrical measurements and VO_{2max} values.

Test Subjects	N = 9
Weight (kg)	76.2 ± 5.4
Height (cm)	182 ± 3.2
Age (years)	21.4 ± 3.1
VO_{2max} -lowland Running ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	73.5 ± 5.3
VO_{2max} -lowland Poling ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	63.7 ± 6.5 *
VO_{2max} -altitude Poling ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	53.8 ± 5.3 * #

Values are listed as means \pm SD. * Significant different from VO_{2max} -lowland Running ($p < 0.01$). # Significant different from VO_{2max} -lowland Poling ($p < 0.01$).

The reason for the strict inclusion criteria's, was to study cross-country skiers with high level of performance customized to high effort exercise. All TS signed a participation agreement which is standardized by the national ethics committee in Norway. TS was aware of the fact that they at any point in the test period could withdraw from the study without any further explanation.

Prior to the inclusion tests, TS were given detailed information about the study, and after this they signed a health declaration on their own health. 10 TS fulfilled the inclusion criteria's, 9 finished the whole study. One got sick during the study, and was excluded from the study.

4.1 Study design

The study was a randomized, cross-over-design, double-blinded, placebo-controlled study. To measure the effect of caffeine ingestion upon the 8 km C-PT at altitude (2000m), one half of the TS ingested caffeine in the first test, the other half placebo. On the second 8 C-PT, TS received the opposite ingestion. Prior to both 8 km C-PT TS were acclimatized to altitude in a hypobaric chamber for 2 hours. During this period, blood samples were drawn from the fingertips of the TS three times. Both the Regional Ethics Committee and the Norwegian Medicines Agency in Norway accepted the study.

4.2 Test Protocol

Table 4.2: Overview of the time schedule for the TS in the study. All testing happened between end of August 2012 – middle of October 2012

Days	What will be done	Time use
Day 1	Inclusion test - Testing of VO_{2max} running and DP. (Lowland)	2:30h
Day 2	Pretest: Submaximal workloads + 8 km C-PT (Lowland)	1:15h
Day 3	Lowland test: Submaximal workloads + 8 km C-PT (Lowland)	1:15h
Day 4	Altitude: Submaximal workloads + VO_{2max} DP	2:45h
Day 5	Altitude: Submaximal workloads + 8 km C-PT (2000m)	3:15h
Day 6	Altitude-test 1: Submaximal workloads + 8 km C-PT at altitude (2000m). Intake of caffeine / placebo	3:15h
Day 7	Altitude-test 2: Submaximal workloads + 8 km C-PT at altitude (2000m). Intake of caffeine / placebo	3:15h

4.2.1 Inclusion test – Testing of VO_{2max} running and DP (Lowland) (Day 1)

At the inclusion test, TS arrived at the Norwegian School of Sports Science (NSSS), and had prior to this been asked to bring normal training clothes. They were also instructed to eat 1.5-2h prior to test. Before the test, TS filled out a declaration of their own health and signed the participation agreement. Anthropometrical measurements as well as age and training status were noted before start. As worm-up TS ran 5.3° at a treadmill during a submaximal incremental test. All subjects started at $8 \text{ km} \cdot \text{t}^{-1}$, and the workload increased by $1 \text{ km} \cdot \text{t}^{-1}$ each fifth minute. Average VO_2 consumption and HR were measured between 2.5-4 minutes at each specific workload. TS were given a 1

minute break between every workload. Blood lactate was drawn from the TS fingertips at each break. Each TS ran four submaximal workloads, hence the last workload were $11 \text{ km} \cdot \text{t}^{-1}$. Before the $\text{VO}_{2\text{max}}$ -running test, each TS were given a 5 minutes long break to drink some water and to walk easy ($4.5 \text{ km} \cdot \text{t}^{-1}$).

At the $\text{VO}_{2\text{max}}$ -test TS ran at a steeper incline (10.5°) than at the submaximal incremental test (5.3°). All TS started at $10 \text{ km} \cdot \text{t}^{-1}$. The speed increased with $0.5 \text{ km} \cdot \text{t}^{-1}$ every 30 seconds. The TS were instructed to run as long as they could, and when they were fatigued, to jump of the treadmill. The average of the two highest 30 s VO_2 measurements was calculated as a TS running $\text{VO}_{2\text{max}}$.

After the running $\text{VO}_{2\text{max}}$ -test TS were given 45 minutes to rest before the $\text{VO}_{2\text{max}}$ -test in double-poling (DP).

TS started to pole at a given velocity of $10 \text{ km} \cdot \text{t}^{-1}$, and the workload increased by 1 km/t every fifth minute. The velocities were chosen due to previous studies on athletes on the same performance levels (Stadheim H K. 2013). Average VO_2 consumption and HR were measured between 2.5-4 minutes at each specific workload. TS were given a 1 minute break between every workload. Blood lactate was drawn from the TS fingertips at each break. Each TS poled four submaximal workloads, hence the last workload were $13 \text{ km} \cdot \text{t}^{-1}$. Before the $\text{VO}_{2\text{max}}$ -DP test, each TS were given a 5 minutes long break to drink some water and to walk easy.

At the $\text{VO}_{2\text{max}}$ -test TS started to DP at a velocity of $12 \text{ km} \cdot \text{t}^{-1}$ also due to previous studies (Stadheim H K. 2013). TS were instructed to increase the speed with $1 \text{ km} \cdot \text{t}^{-1}$ every 30 seconds, and to continue to do so until fatigue. The average of the two highest 30 s VO_2 measurements was calculated as a TS DP $\text{VO}_{2\text{max}}$.

4.2.2 Lowland test: Submaximal workloads + 8 km C-PT (Day 3)

At the submaximal incremental test, all subjects DP at velocities corresponding 55%, 60%, 65% and 70% of their individual DP $\text{VO}_{2\text{max}}$. This was calculated using linear regression from the incremental test from day 1.

TS started to pole at the given velocities, and the workload increased every fifth minute. Average VO_2 consumption and HR were measured between 2.5-4 minutes at each specific workload. TS were given a 1 minute break between every workload.

Blood lactate was drawn from the TS fingertips at each break. All TS was also asked about RPE and pain (arms and legs) at the end of every workload. Before the 8 km C-PT, each TS were given a 5 minutes long break to drink some water and to walk easy. After this break, and right before start of the 8 km C-PT all TS was asked about their pain both in their arms and in legs.

At the 8 km C-PT, TS were blinded on everything except the remaining distance, which was counting descending. Time and HF was noted every kilometer. During the 8 km C-PT all TS was asked about their RPE and pain (upper body and lower body) at 3 km, 5 km, 7 km and immediately after they finished (8 km). VO_2 measurements were measured the first 2 minutes, after 3.5 kilometer, and the last 0.5 kilometer. Right after the 8 km C-PT blood was drawn from the TS fingertips in order to measure blood lactate.

4.2.3 Altitude: Submaximal workloads + VO_{2max} DP (Day 4)

VO_{2max} decreases with 4.6 to 7.5 % per 1000 meters above sea-level (Wehrin & Hallèn, 2006), and performance are strongly correlated with VO_{2max} . Velocities at altitude during the submaximal workloads were reduced to make the workloads comparable to the same test in lowlands.

TS started to pole at a given velocity of $9 \text{ km} \cdot \text{t}^{-1}$, and the workload increased by $1 \text{ km} \cdot \text{t}^{-1}$ every fifth minute. Average VO_2 consumption and HR were measured between 2.5-4 minutes at each specific workload. TS were given a 1 minute break between every workload. Blood lactate was drawn from the TS fingertips at each break. Each TS poled four submaximal workloads, hence the last workload were $12 \text{ km} \cdot \text{t}^{-1}$. Before the VO_{2max} -DP test, each TS were given a 5 minutes long break to drink some water and to walk easy.

At the VO_{2max} -test TS started to DP at a given velocity of $11 \text{ km} \cdot \text{t}^{-1}$. TS were instructed to increase the speed with $1 \text{ km} \cdot \text{t}^{-1}$ every 30 seconds, and to continue until fatigue. The average of the two highest 30 s VO_2 measurements was calculated as a TS DP VO_{2max} .

VO_{2max} DP in altitude compared to VO_{2max} DP in lowland were significantly decreased (from $63.7 \pm 6.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $53.8 \pm 5.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ($p < 0.01$).

4.2.4 Altitude: Submaximal workloads + 8 km C-PT (Day 6 and 7)

Subjects entered the hypobaric chamber and air pressure was reduced to 800 mbar corresponding to 2000 meters above sea-level.

5 minutes after entry in the altitude-chamber both a venous blood sample and a blood sample from the fingertips were drawn

The incremental test was similar to the incremental test at lowland, but velocities were adjusted to VO_{2max} at altitude using linear regression from day 4. At the submaximal incremental test, all TS DP at velocities corresponding 55%, 60%, 65% and 70% of their individual DP VO_{2max} in altitude.

TS started to pole at the given velocities, and the workload increased every fifth minute. Average VO_2 consumption and HR were measured between 2.5-4 minutes at each specific workload. Blood lactate and blood glucose was drawn from the TS fingertips at each break. All TS was also asked about RPE and pain (upper and lower body) at the end of every workload. TS were given a 1 minute break between every workload. Before the 8 km C-PT, each TS was given a 5 minutes long break to drink some water and to walk easily. After this break, and right before start of the 8 km C-PT all TS was asked about their pain both in their upper and lower body.

At the 8 km C-PT, TS were blinded on everything except the remaining distance as at lowland. Time and HR was noted every kilometer. During the 8 km C-PT all TS was asked about their RPE and pain (upper body and lower body) at respectively 3 km, 5 km, 7 km and immediately after they finished (8km). VO_2 measurements were measured the first 2 minutes, after 3.5 kilometer, and the last 0.5 kilometer. Right after the 8 km C-PT both venous blood and s blood sample from the TS fingertips were drawn in order to measure adrenaline, blood lactate, bicarbonate and blood glucose.

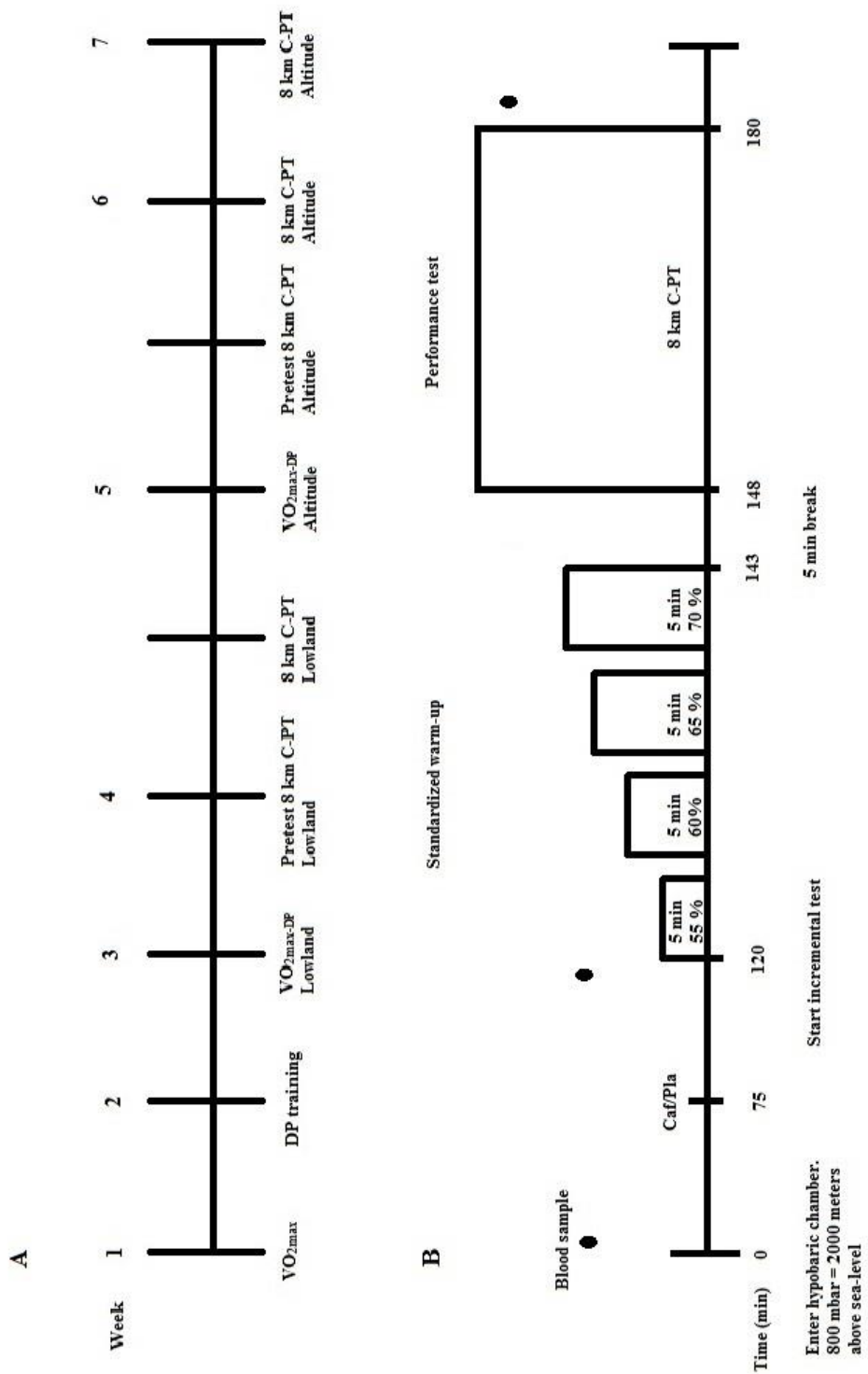


Figure 4.1: A. Flow chart showing all the tests. B. Time-schedule of the main test-day in altitude

4.3 Food and liquid consumption prior to main tests

The last 48 hours prior to the main tests, TS was asked to reduce intake of caffeine containing products. TS were not allowed to drink any coffee or use other caffeine products 12 hours prior to the main tests.

TS were asked to register all food and drink the last 24 hours prior to the main tests. They were also advised to eat and drink the same meal before each main test. Caffeinated products were

4.4 Training prior to main tests

Prior to the main test, TS was advised to only perform low intensity training (55-70 % of HR_{max}) the last 48 hours before the main tests. TS filled out a questionnaire about what type of exercise they had completed in the same period.

4.5 Equipment

4.5.1 Hypobaric chamber

The hypobaric chamber (Norsk undervannsteknikk A/S, Haugesund, Norge) at the Norwegian School of Sport Sciences (NSSS) was used during all main tests. During testing at acute hypoxia, air pressure was reduced to 800 mBar. This is equivalent to 2000 meters above sea-level at 17° C.

During the first two hours of resting $0.5 \text{ l} \cdot \text{min}^{-1}$ oxygen were added to cover the use of oxygen by TS and the test-leader. During physical activity the consumption of oxygen increases, thus more oxygen were added into the chamber to keep the concentration stable. On the basis of the pretests, approx. $3 \text{ l} \cdot \text{min}^{-1}$ of extra oxygen were added to cover the enhanced usage of oxygen during physical activity.

Three gas scrubbers containing sofnolime-filters and circulating fans worked as CO_2 -traps to ensure a stable CO_2 concentration. During hard physical activity CO_2 production from the subjects exceeded the capacity of CO_2 -removal of the three scrubbers. This resulted in an enhanced CO_2 concentration of the air inside the chamber. The concentrations of both O_2 and CO_2 were under constant supervision and even though CO_2 -concentration increased it never exceeded 0.08 %. During rest and at lowland CO_2 concentrations were as expected 0.04 %. However, this was not considered dangerous for the subjects, or influencing the results.

4.5.2 Measurements of oxygen uptake and RER

At lowland Oxycon Pro (Jaeger, Hoechberg, Tyskland) was used to conduct mean oxygen measurements. During the VO_{2max} running test a Woodway treadmill was used (PPS 55 Sport Woodway inc, USA).

In the hypobaric chamber, VO_2 and VE were measured using V_{max29} (Sensormedics, USA). The V_{max29} were calibrated towards the Oxygen Pro before study start.

The equipment for measurement of VO_2 were calibrated with mixture gasses with known amount of O_2 and CO_2 (14.93% O_2 and 5.99 % CO_2) and normal air (approx 20.90 % O_2 and 0.04 % CO_2) in both altitude and in lowland. Volume was calibrated manually using a pump containing 3 liters of volume (Calibration Syringe, Series 5530, Hans Rudolph Inc., MO, USA).

During testing, TS used a V2 mask (Hans Rudolph Instr., USA) which covered the mouth. A nose bracket was used to stop breathing thru the nose. Expired air was led thru a hose into the mixing chamber (Oxycon Pro) and analyzed with a turbine (Triple V volume transducer). The total uncertainty of this ergo spirometri measurements are $\pm 3\%$ (Åstrand, 2003).

During the 8 km C-PT there were methodical problems with getting the mask into the TS mouth. Double-poling is a technique with much movement in vertical direction, and the mask often slipped out of the TS mouth. VO_2 -data from the 8 km C-PT was therefore excluded from the study.

4.5.3 Lactate measurements

The lactate analyzer used was YSI 1500 Sport Lactate Analyzer (Yellow Spring Instruments, USA). The fingers were punctured by a Saft-T-Pro Plus (Accu-Check, Mannheim, Tyskland) and the blood were drawn into a 50 μ l capillary tube. The blood was then drawn into the analyzer by a 20 μ l pipette. The analyzer was calibrated with a 5.0 $mmol \cdot l^{-1}$ lactate stock solution before each test and between the submaximal workloads and main tests. Values between 4.95 $mmol \cdot l^{-1}$ and 5.05 $mmol \cdot l^{-1}$ was accepted. Under normal circumstances the uncertainty of measurements are $\pm 2\%$

regarding blood lactate values between 0 and 5 mmol • l⁻¹ and ± 3 % regarding values between 5 and 15 mmol • l⁻¹.

4.5.4 Heart rate measurements

Heart rate (HR) was measured using a heart rate monitor (Polar RS 800, Finland). The error of measurement stated by the producer is ± 1 %.

4.5.5 Glucose measurements

Blood glucose was measured in capillary blood. The fingertip was cleaned before punctured (Accu-Check, Safe-T-Pro Plus; Mannheim, Germany). The first drop of blood was drawn away before filling the Microcuvets (HemoCue Glucose 201) with blood. These microcuvets was placed in a HemoCue Glucose 201⁺ (HemoCue Glucose 201⁺, Ängelholm, Sweden) and analyzed. Measurements take 40-240 seconds.

4.5.6 Blood bicarbonate measurements

Blood bicarbonate was measured using a ABL 80 Flex (Radiometer, Brønshøj, Denmark). The fingers were punctured by a Saft-T-Pro Plus (Accu-Check, Mannheim, Tyskland) and the blood were drawn into a 125 µl capillary tube.

4.5.7 Thorax Trainer – Cross-country poling ergometer

The cross-country poling instrument used in the study was a Thorax Trainer Elite (Denmark). The machine works by using air resistance the same way as a rowing machine. Air pressure was measured before every test to ensure the same resistance. Of the 10 possible levels, the Thorax Trainer was set to level 1 (easiest) because this resistance gave the best comparison basis to the frequency used in cross-country. The parameters registered by the Thorax Trainer was: Strokes, power (watt), speed (km • t⁻¹), distance and time usage.

The ski poles used in all test was Swix CT1 (Lillehammer, Norway). The length of the poles was 85 % of the height of the TS.

4.6 Other information

Form of the day, motivation, sleep and eating patterns were evaluated by a questionnaire. TS noted from 0 to 100 how their form of the day and motivation was prior to the test, after the submaximal workloads and after the test. Eating patterns and physical activity the last 48 h was noted during the 2 hours of rest before the submaximal incremental test.

4.7 Statistics

Microsoft Excel 2007 was used to perform statistical analyses of the results from the study. To compare differences in endurance performance, t-test for paired samples was used. Magnitude based statistics were also used. All data in the study are presented as standard deviation (SD) and the significant level was set to $p < 0.05$

5.0 Results

Mean performance for the 8 km C-PT at lowland (NSSS altitude, 180 meters above sea level) were in average 1 minute and 46 seconds better than the mean performance time with placebo in altitude (Figure 1) and corresponds to an increase in time of 5.5 % The increase in time to complete the 8 km C-PT between the caffeine treatment (in altitude) and lowland was 4.2 %, corresponding 1 minute and 17 seconds.

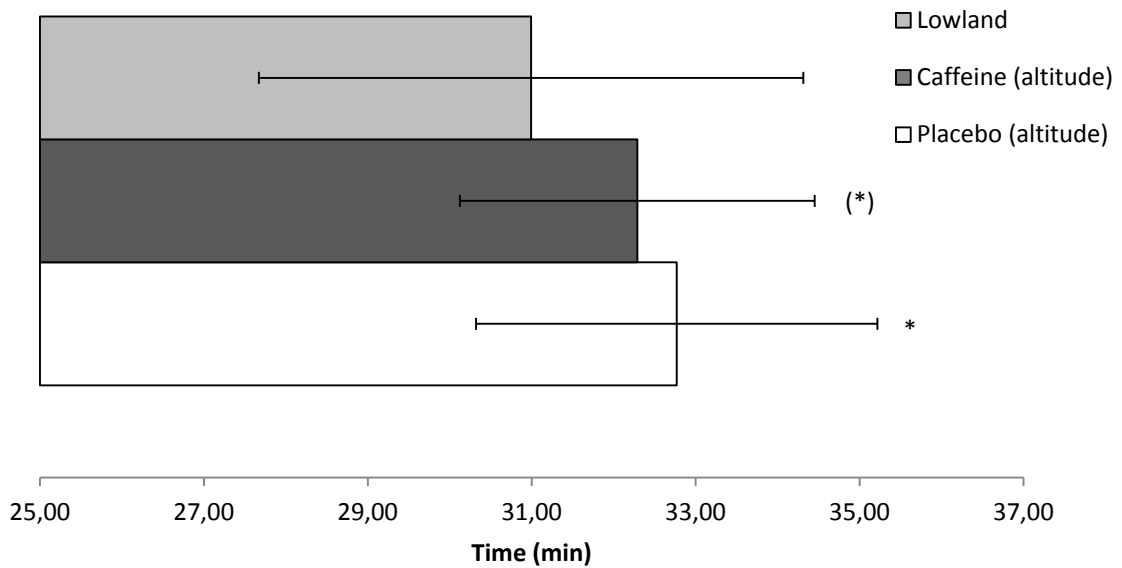


Figure 5.1: Average time to complete the 8 km C-PT in altitude with caffeine and placebo treatment compared to the 8 km C-PT at lowland. Values are listed as means \pm SEM.

* Significant different form the 8 km C-PT in lowland ($p < 0.01$). (*) Significant different from the 8 km C-PT in lowland ($p < 0.1$). Values are listed as mean \pm SD

5.1 Time usage at the 8 km C-PT

Table 5.1 shows the average time used ($\text{min} \cdot \text{km}^{-1}$) for every kilometer, as well as total time for the 8 km C-PT in altitude. The respective values from caffeine and placebo treatments are listed as means \pm SD, % difference and effect size (90% confidence limits). Also listed is qualitative inference.

Time to complete the 8 km C-PT on average decreased 25 ± 36 seconds (possibly effect) after caffeine ingestions compared to placebo (table 5.1). Of the 9 TS, 7 completed the 8 km C-PT faster after caffeine ingestion, while 2 TS used shorter time

on the placebo trial. The average speed during each km in the 8 km C-PT shows a gradual fall for both groups from start to finish (Table 5.1). Mean time for the first 3 kilometers (0-3km) was 18 ± 15 s faster after caffeine ingestion compared to placebo ($2.54\% \pm 2.13\%$, mean \pm 90% confidence limits). This difference was not seen on the last 5 kilometers (3-8km), where the average difference between the treatments was only 7 ± 27 seconds.

Table 5.1: Performance measurements for the 8 km C-PT at altitude.

	Caffeine Time (min • km⁻¹)	Placebo Time (min • km⁻¹)	% difference (90% CL)	Effect size (90% CL)	Qualitative inference	P- values
1 km	3.78 ± 0.23	3.86 ± 0.19	2.18 ± 2.25	0.34 ± 0.36	Likely	0.14
2 km	3.89 ± 0.28	4.01 ± 0.28	3.19 ± 2.17	0.40 ± 0.27	Very likely	0.03
3 km	3.99 ± 0.29	4.08 ± 0.32	2.24 ± 2.58	0.27 ± 0.31	Likely	0.15
4 km	4.11 ± 0.28	4.14 ± 0.38	0.74 ± 2.76	0.09 ± 0.32	Unclear	0.58
5 km	4.10 ± 0.31	4.15 ± 0.39	1.11 ± 3.10	0.12 ± 0.33	Unclear	0.49
6 km	4.16 ± 0.32	4.19 ± 0.35	0.48 ± 2.27	0.06 ± 0.26	Unclear	0.67
7 km	4.19 ± 0.32	4.18 ± 0.33	-0.15 ± 2.58	-0.02 ± 0.30	Unclear	0.92
8 km	4.14 ± 0.38	4.16 ± 0.32	0.65 ± 2.24	0.07 ± 0.26	Unclear	0.69
Total	32.36 ± 2.24	32.78 ± 2.45	1.27 ± 1.85	0.16 ± 0.24	Possibly	0.24

Data are given as mean \pm SD.

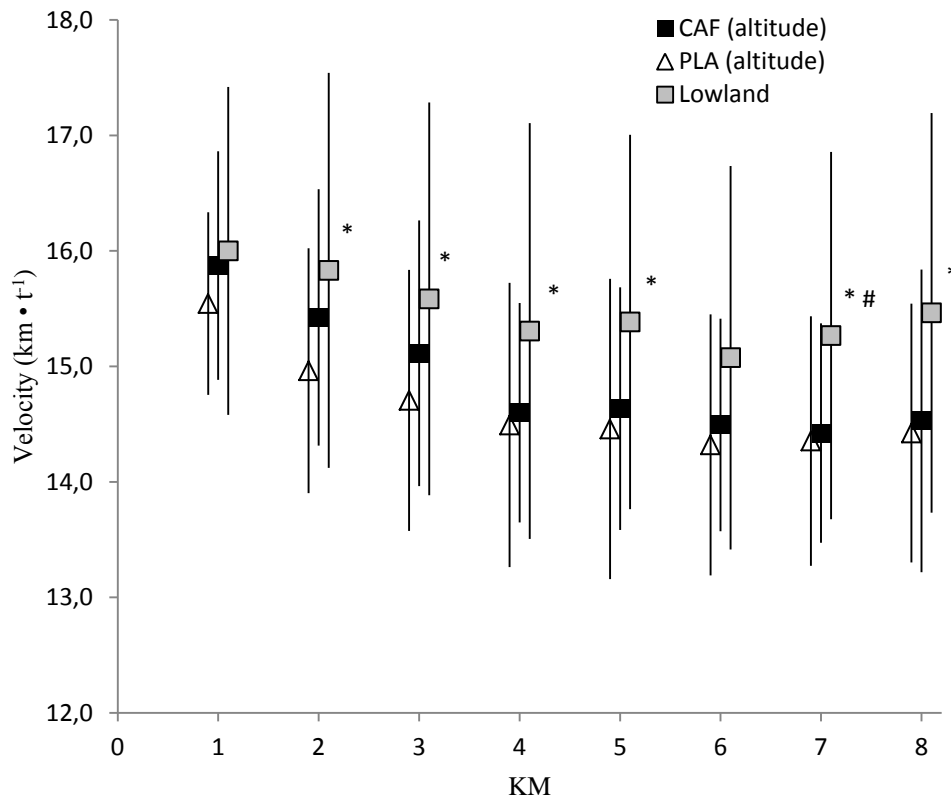


Figure 5.2: Average velocity on the different kilometers on the 8 km C-PT with and without caffeine ingestion. Values are listed as means \pm SD. * Significant different from placebo at altitude ($p < 0.05$). # Significant difference between lowland and caffeine at altitude ($p < 0.05$)

5.2 Physiological parameters

Table 5.2: Physiological measurements after the 8 km C-PT in altitude.

Measure	Caffeine (mean \pm SD)	Placebo (mean \pm SD)	% difference (90% CL)	Effect size (90% CL)	Qualitative inference	P - values
Plasma Caffeine	28.12 \pm 7.6	0.74 \pm 0.84		4.47 \pm 0.89	Very likely	0.000001
Adrenaline	3.6 \pm 2.2	1.7 \pm 0.8	89.4 \pm 55.2	0.56 \pm 0.38	Very likely	0.16
La _{Post}	8.3 \pm 1.8	6.4 \pm 1.4	-22.55 \pm 16.88	-1.10 \pm 0.67	Very likely	0.02
Glucose _{Post}	8.1 \pm 1.8	6.7 \pm 1.5	-17.71 \pm 9.44	-0.8 \pm 0.37	Very likely	0.01
HR _{max}	184 \pm 7	180 \pm 5	-2.20 \pm 1.67	-0.58 \pm 0.43	Very likely	0.04
pH _{post}	7.29 \pm 0.05	7.33 \pm 0.03	0.55 \pm 0.23	0.85 \pm 0.35	Very likely	0.002

Data are given as mean \pm SD. Lactate (La⁻), Heart rate (HR). Adrenaline measurements (n=3)

During the 8 km C-PT, HR was significant higher at every kilometer of the test after caffeine ingestion compared to placebo (figure 5.3). The HR_{Peak} , in which all TS reached at the end of the test, were very likely higher ($2.2\% \pm 1.67\%$, mean \pm 90% confidence limits) after caffeine ingestion (Table 5.2).

Caffeine ingestions very likely resulted in increased blood lactate (BLa^-) levels immediately after the 8 km C-PT (table 5.2) compared to placebo. On average TS had $1.8 \pm 1.2 \text{ mmol} \cdot \text{l}^{-1}$ higher after caffeine ingestions than after placebo.

The blood glucose drawn immediately after the 8 km C-PT showed a $1.4 \pm 0.8 \text{ mmol} \cdot \text{l}^{-1}$ higher concentration after caffeine ingestion compared to placebo (Table 5.2).

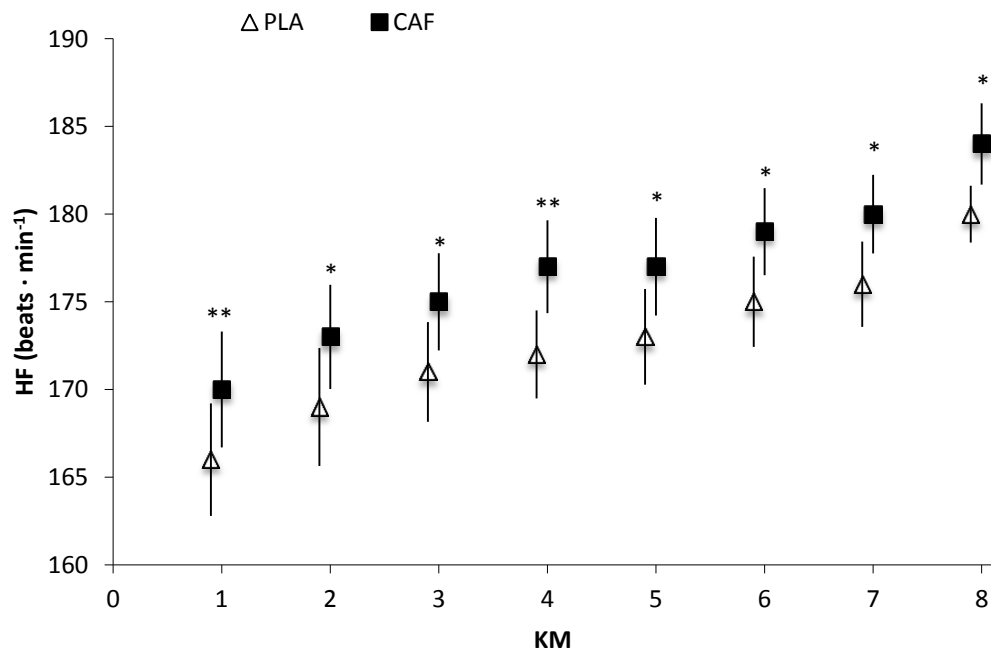


Figure 5.3: Average heart rate during the 8 km C-PT with and without caffeine ingestion. Values are listed as means \pm SD. * Significant difference between treatments ($p < 0.05$). ** Significant difference between treatments ($p < 0.01$).

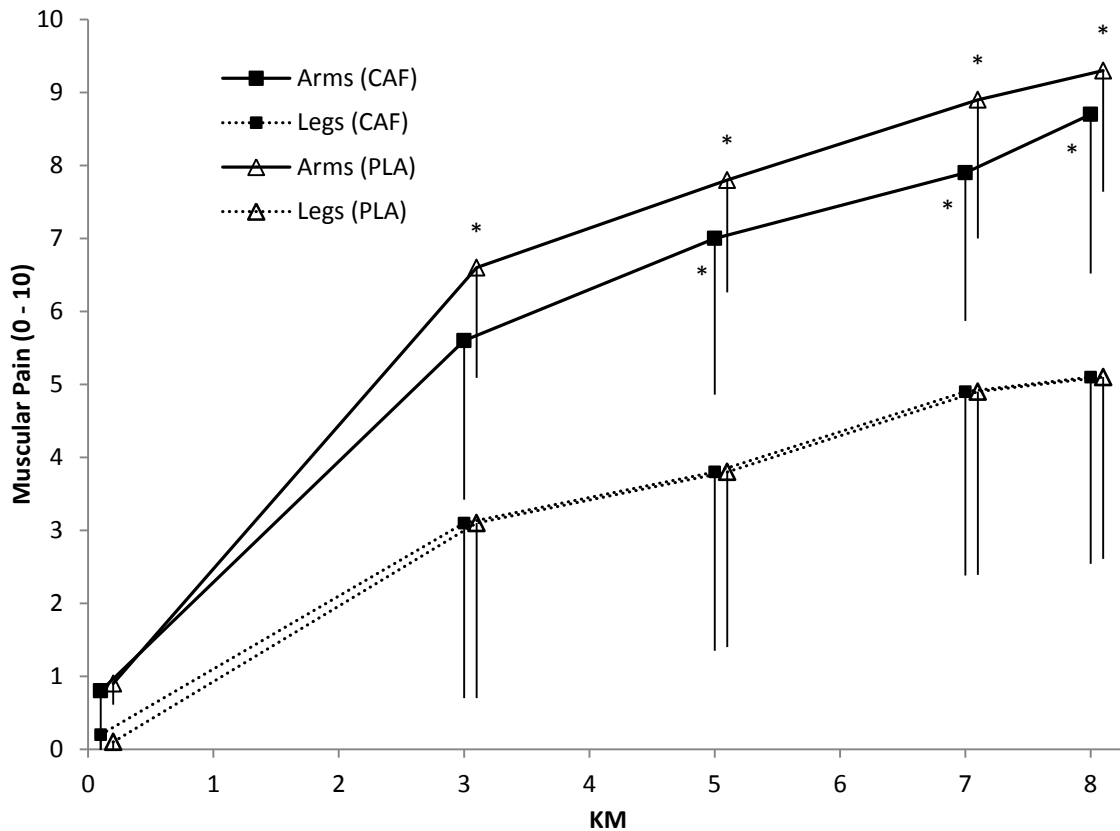


Figure 5.4: Average muscular pain in arms and legs during the 8 km C-PT with and without caffeine ingestion. Values are listed as means \pm SD. * Significant difference in muscular pain between arms and legs ($p < 0.05$).

Muscular pain in the upper body and arms did not differ between the treatments (figure 5.4). The TS reported significantly more pain in the upper body than in the legs throughout the test regardless of the treatment. No differences in muscular pain between the treatments were reported in the legs.

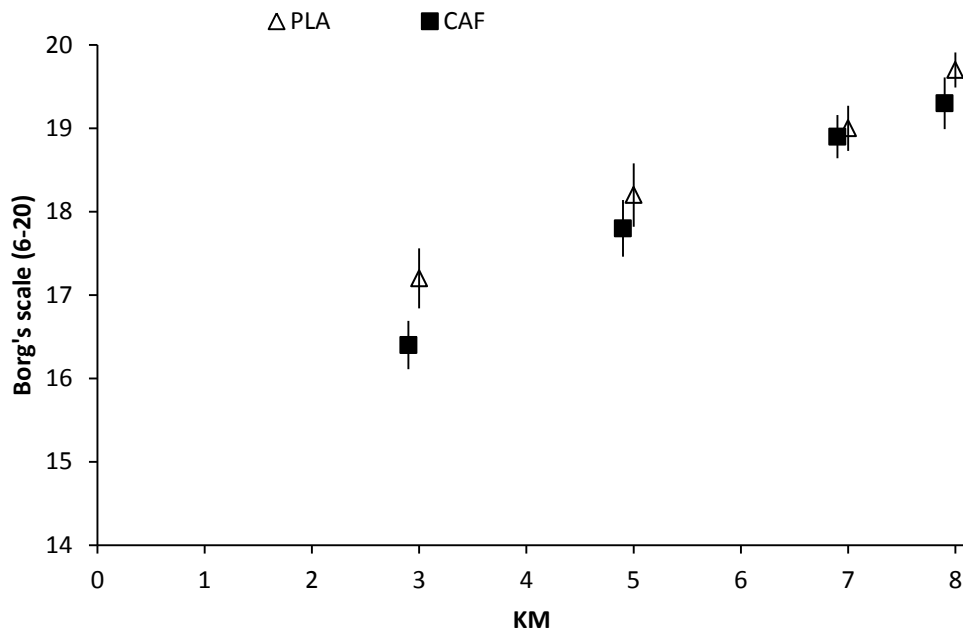


Figure 5.5: Average RPE during the 8 km C-PT with and without caffeine ingestion. Values are listed as means \pm SD. * Significant difference between treatments ($p < 0.05$).

RPE increased gradually during the 8 km C-PT and reached a score of 19.3 ± 0.97 (CAF) and 19.7 ± 0.66 (PLA) at the end of the performance test. No differences in rate of perceived exertion (RPE) were reported during the 8 km C-PT between the treatments.

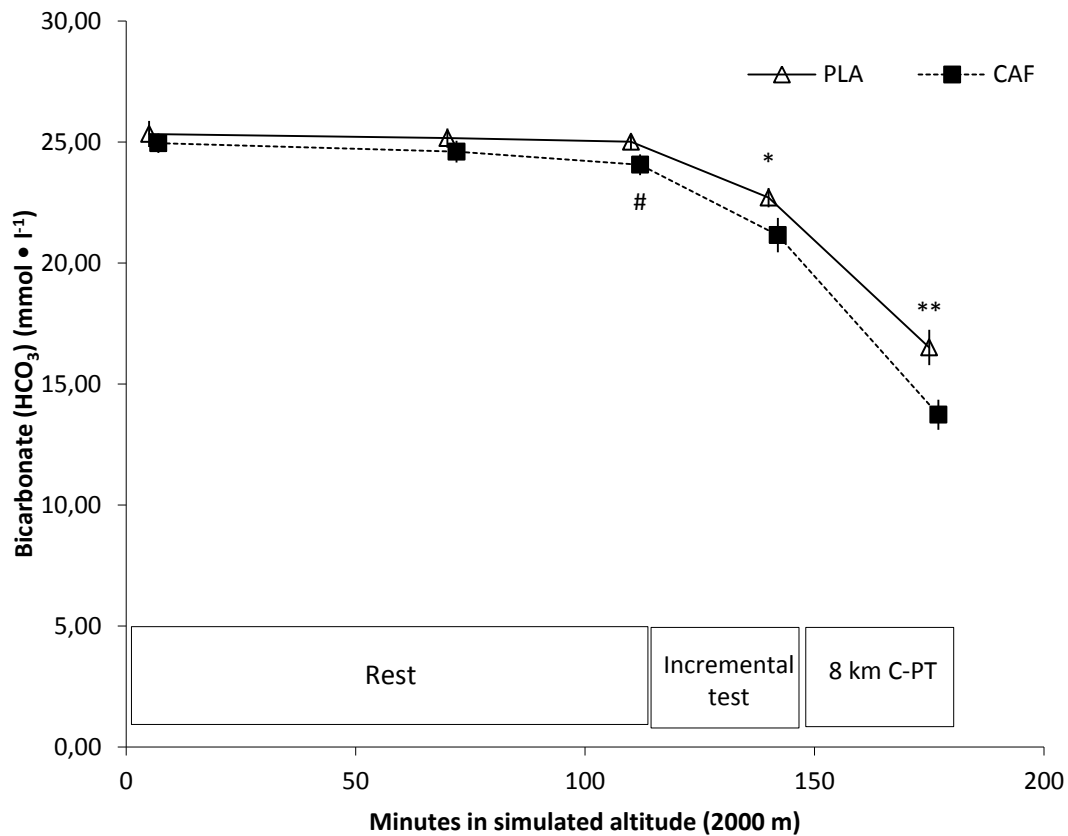


Figure 5.6: Average bicarbonate values at 2000 meters above sea-level before and during the performance tests with and without caffeine ingestion. Values are listed as means \pm SD. * Significant difference between treatments ($p < 0.05$). ** Significant difference between treatment ($p < 0.01$). # Significant different from initial bicarbonate level following the same treatment ($p < 0.05$).

Blood bicarbonate (HCO_3^-) sampled after the 8 km C-PT showed that caffeine ingestions caused a larger decrease in blood bicarbonate compared to placebo (Figure 5.6). The bicarbonate level was not different between the treatments before the incremental tests. The concentration of bicarbonate was significantly lowered before the submaximal incremental test following caffeine ingestion ($p < 0.05$). After placebo ingestion no significant decrease in bicarbonate before the submaximal workloads.

Table 5.3: Physiological data during the submaximal incremental test

	Resting 2 h in altitude	55% of $\dot{V}O_{2max}$ = $10.8 \pm 1.16 \text{ km} \cdot \text{t}^{-1}$	60% of $\dot{V}O_{2max}$ = $11.7 \pm 1.17 \text{ km} \cdot \text{t}^{-1}$	65% of $\dot{V}O_{2max}$ = $12.3 \pm 1.0 \text{ km} \cdot \text{t}^{-1}$	70% of $\dot{V}O_{2max}$ = $13.2 \pm 1.05 \text{ km} \cdot \text{t}^{-1}$
$\dot{V}O_2$ ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Caffeine Placebo	30.1 ± 3.4 28.7 ± 3.0	33.4 ± 3.2 32.4 ± 4.7	35.5 ± 3.4 34.2 ± 4.4	37.9 ± 4.2 38.5 ± 6.0
HR (beats $\cdot \text{min}^{-1}$)	Caffeine Placebo	125 ± 8.6 123 ± 10.2	134 ± 11.2 135 ± 8.2	142 ± 9.7 141 ± 8.4	150 ± 9.7 149 ± 7.3
Lactate (mM)	Caffeine Placebo	2.23 ± 0.75 1.79 ± 0.37	$2.34 \pm 0.75^*$ 1.76 ± 0.43	$2.45 \pm 0.72^{**}$ 1.86 ± 0.56	$2.65 \pm 0.76^{**}$ 2.13 ± 0.65
Glucose (mM)	Caffeine Placebo	4.91 ± 0.59 4.61 ± 0.77	$4.68 \pm 0.60(^*)$ 4.36 ± 0.75	4.71 ± 0.67 4.58 ± 0.81	4.51 ± 0.59 4.53 ± 0.68
HCO_3^- (mM)	Caffeine Placebo	$24.1 \pm 1.3(^*)$ 25.1 ± 1.0			$21.1 \pm 2.2^*$ 22.7 ± 1.3
RPE (6-20)	Caffeine Placebo	$8.6 \pm 0.6(^*)$ 9.6 ± 0.4	$9.8 \pm 0.5^*$ 10.9 ± 0.3	$11.2 \pm 0.4(^*)$ 11.9 ± 0.3	$12.5 \pm 0.4(^*)$ 13.1 ± 0.3
Muscular pain arms (1-10)	Caffeine Placebo	1.9 ± 0.9 $1.2 \pm 1^*$	2.3 ± 0.9 $1.8 \pm 1.1^*$	2.4 ± 1.0 2.1 ± 1.3	3.1 ± 1.1 $2.6 \pm 1.2^*$
Muscular pain legs (1-10)	Caffeine Placebo	0.1 ± 0.3 0.3 ± 0.5	0.2 ± 0.4 0.3 ± 0.5	0.3 ± 0.6 0.6 ± 0.7	0.6 ± 0.7 0.6 ± 0.7

Data are given as mean \pm SD. * Significant difference between the treatments ($p < 0.05$). ** Significant difference between the treatments ($p < 0.01$). (*.) Significant difference between the treatments ($p < 0.1$)

5.3 Submaximal incremental test

Caffeine ingestions also led to elevated levels of blood lactate during the submaximal workloads in the incremental test (Table 5.3). The TS started the 8 km C-PT with elevated levels of blood lactate ($p < 0.01$).

Caffeine ingestions elicited no differences in heart rate (HR) during the incremental test before the 8 km C-PT at 2000 m altitude. No differences in blood glucose were found between the treatments during the two resting hours before the test. Of the blood samples drawn during the incremental test, only the second of the four samples showed higher concentration of glucose after caffeine ingestion compared to placebo ($p < 0.05$).

No differences were observed in neither oxygen uptake nor blood glucose during the incremental test between the treatments. After the last submaximal workload (70 % of VO_{2max}), a significant decrease in bicarbonate following caffeine ingestion was observed ($p < 0.05$).

In the incremental test before the 8 km C-PT, there was a tendency towards decreased RPE following caffeine ingestion. Statistical difference ($p < 0.05$) were however only observed on one (60%) of the four submaximal workloads. However, RPE tended to be lowered at the 3 other submaximal workloads following caffeine ingestion as well ($p < 0.1$) (table 5.3). Muscular pain in the arms was significantly lower following caffeine ingestion compared to placebo in three of the four submaximal workloads (table 5.3). No differences were observed in muscular pain in the legs between the treatments. Muscular pain was significantly higher in the arms compared to the legs after both treatments ($p < 0.01$).

5.4 Other results

No differences was observed between form of the day, motivation, amount of sleep or eating pattern before the different treatments. In the questionnaire prior to the test, TS noted 69 ± 12 on form of the day after caffeine ingestion, and 69 ± 4 after placebo treatment. At the same tests, motivation was 80 ± 10 and 78 ± 13 with and without caffeine ingestion.

6.0 Discussion

The main finding of the present study was that ingestion of $4 \text{ mg} \cdot \text{kg}^{-1}$ caffeine caused a small and possible enhancing effect on endurance poling performance in altitude. On average caffeine ingestion improved the time to complete the 8 km C-PT by 1.3 %, and 7 out of the 9 TS demonstrated this enhancing effect (figure 5.1). Importantly, caffeine ingestion significantly improved velocity during the first 3 kilometers of the 8 km C-PT ($p < 0.05$), whereas velocity did not differ during the last 5 kilometer. As expected TS used more time to complete the 8 km C-PT in altitude compared to the same test in lowland. After placebo treatment TS used 5.5 % more time to complete the 8 km C-PT, and after caffeine ingestion TS increased the time use by 4.2 % compared to the test in lowland. Only the placebo trial significantly differed from the lowland-test ($p < 0.05$).

Blood lactate was significantly higher after caffeine ingestion compared to placebo after the 8 km C-PT (table 5.2). This result is consistent with other caffeine studies conducted in lowland (Stadheim et al., 2013; Stadheim et al., 2014). The increased lactate concentrations support that subjects showed a larger anaerobic capacity after caffeine ingestion. Blood bicarbonate levels were significantly lower after the 8-km CPT after caffeine ingestion compared to placebo also indicating larger anaerobic work. RPE and muscular pain did not differ between the treatments during the 8 km C-PT. During a maximal performance task as the present, TS are pushing as hard as possible, and the lack of differences in RPE and muscular pain are in consistence with other studies (Stadheim et al., 2013; Stadheim et al., 2014; Irwin et al., 2011).

6.1 Caffeine, performance and altitude

Caffeine ingestions prior to endurance competitions are common among athletes (Burke, 2008; Tarnopolsky, 1994). Many studies have observed improved performance after caffeine ingestions. Most common duration of endurance performances in scientific research showing positive effect after caffeine ingestion, are between 30-60 minutes (Stadheim, 2013; Dean et al., 2009). The average duration of the 8 km C-PT in altitude of this study was 32.36 ± 2.24 min (CAF) and 32.78 ± 2.45 and (PLA) therefore comparable to other research. Additionally the average time use of the same test in lowland was 30.99 ± 3.32 min. Cyclists and runners are often used as test subjects, but

Stadheim et al., (2013) used an 8 km C-PT DP to research the effect of $6 \text{ mg} \cdot \text{kg}^{-1}$ caffeine on 10 cross-country skiers where caffeine significantly increased performance ($p < 0.05$). In Stadheim et al (2013) a 5 % improved performance was observed following caffeine ingestion. The enhanced performance by the test subjects after caffeine ingestions were suggested due to increased ability to push themselves harder. In Stadheim et al., (2014) TS double-poled a significant longer distance during a 10 min all-out C-PT following caffeine ingestion. These results was confirmed when the TS repeated the all-out C-PT at the consecutive day. In the same study the researchers observed the same enhancing pattern from two different dosages of caffeine ingestion ($3 \text{ mg} \cdot \text{kg}^{-1}$ and $4.5 \text{ mg} \cdot \text{kg}^{-1}$) compared to placebo. In both studies Stadheim et al., (2013) and Stadheim et al., (2014) use the same type of methods and TS as the present study, thus results from both studies are comparable to this study. In fact Stadheim et al., (2013) use the same 8 km C-PT as the present study.

Caffeine consumption prior to exercise have been reported beneficial in studies using time-trials (TT) (Dean et al., 2009; Ivy et al., 2009; Stadheim H K. 2013), time to exhaustion (TTE) (Ping et al., 2010) and when a fixed amount of work is conducted in shortest possible of time (Ormsbree et al., 2014). Some authors find caffeine's ergogenic effects more apparent on well-trained athletes compared to untrained individuals (Astorino, Cottrell, Talhami Lozano, Aburto-Pratt & Duhon, 2012). The present study used highly-trained cross-country athletes ($\text{VO}_{2\text{max-running}} = 73.5 \pm 5.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). As the 8 km C-PT used in this study is a time-trial (TT) the basis of comparison are on studies using TT as a method of investigating the effect of caffeine on the respective performance. Both Dean et al. (2009) and Ivy et al. (2009) investigated how caffeine ingestions prior to a TT affected the performance in cycling. Both authors found enhanced performance after caffeine ingestions compared to placebo. Where Dean et al., (2009) investigated the effects of caffeine on a 40 min time-trial, Ivy et al., (2009) used the time to complete a standardized amount of work equal 1 hour of cycling at 70 % of $\text{VO}_{2\text{max}}$. Caffeine normally has an enhancing effect upon EP lasting 20-120 minutes (Ping et al., 2010; Irwin et al., 2011).

In the present study 7 of the 9 TS improved performance following caffeine ingestion. Stadheim et al., (2013) observed the same pattern with 8 out of 10 TS improving their performance due to caffeine ingestion. In Stadheim et al., (2014) 7 of

the 8 TS decreased the time use on a 8 km C-PT following caffeine ingestion. Due to these athletic-specific findings researchers have studied genetics in order to search for differences regarding the different effects of caffeine on performance (Womack, 2012). Evidence suggests there might be both responders and non-responders to caffeine based on human genetics and humans with a specific polymorphism of the gene CYP1A2 are more sensitive to caffeine compared to humans without this polymorphism. In this study no tests of human genetics was investigated, but 2 of the TS did not have any enhancement of performance after caffeine ingestion. If the remaining 7 TS have the specific polymorphism is not known by the author.

Despite the many studies on caffeine in lowland, few studies are conducted on how caffeine affects an endurance performance in altitude. Hemmingson & Berglund (1982) and Fulco et al., (1994) are the only two studies on the topic as far as the author know. Fulco and colleagues (1994) found a 54 % ($p < 0.01$) increase in time to exhaustion following caffeine ingestion when cyclists were exposed to acute hypoxia. No differences in time to exhaustion were found during chronic hypoxia when comparing caffeine and placebo. Hemmingson & Berglund (1982) investigated effects of caffeine on race-time on a 21 km cross-country skiing race on 300 and 2.900 meters above sea-level. Caffeine ingestion decreased time to complete the 21 km by 3.18 % at altitude. They found no evidence of caffeine enhancing effects at 300 meters above sea-level. This study does have some methodical problems. As all tests are conducted outside, weather, temperature and other interfering factors might not be the same on all tests. As snow conditions rarely are the same in lowland compared to altitude, the skis used in the study would never affect the results in the same way two times in a row. However, the study was specific regarding impact of caffeine on cross-country performance. Also the results of the two (Fulco et al., 1994; Hemmingson & Berglund, 1982) studies are similar to the present study regarding performance after caffeine ingestion in altitude.

As the human body is exposed to the lowered oxygen pressure in altitude, some physiological adaptations occur. One of the initial physiological responses is increased ventilation, often termed hypoxic ventilatory response (HVR).

6.2 Caffeine – mechanisms of action

Although caffeine ingestions have proven beneficial on endurance performance, the mechanisms of actions are not clear (Costill et al., 1978; Stadheim et al., 2013; Stadheim et al., 2014). Enhanced endurance performance has been suggested to be due a glycogen sparing and / or reduced perception of pain following caffeine ingestion. Glycogen sparing would result in increased utilization of fat and therefore changes in RER (Costill et al., 1978). The increased adrenaline concentrations following caffeine ingestion were suggested to increase fat oxidation and therefore spare glycogen. When performing to exhaustion, spared glycogen would allow TS to work for a longer duration. This theory was more central 30 years ago. The present study, in addition to other more recent studies, found no changes in RER-values during the submaximal workloads following caffeine ingestion (Stadheim et al., 2013; Graham, 2001).

One theory behind the improved performance following caffeine ingestion is caffeine affecting the central nervous system (CNS) by blocking adenosine receptors. In turn this might result in lowered perception of pain and increasing HR (Goldstein et al., 2010).

6.3 Pain and Rate of Perceived Exertion (RPE)

Results show no significant differences in RPE during the 8 km C-PT between the two treatments (Figure 5.5). These results are consistent with results reported in other TT studies (Irwin et al., 2011). In the study of Irwin et al., (2011), cyclist completed a 60 minute TT with higher average speed after caffeine ingestion compared to placebo. Throughout the TT, no differences were observed in RPE between the treatments. On an 8 km running test, Bridge & Jones (2006) investigated how caffeine ingestion affected different physiological variables including RPE. They report a trending lowered RPE during the 8 km, but no significant differences were conducted. Because a TT protocol implies TS are pushing themselves as hard as possible, the lack of differences found in RPE between caffeine and placebo might not be unusual. The interesting aspect is the higher work intensity found following caffeine ingestions do not accompany any enhanced RPE.

Pain was significantly higher in the arms compared to the legs during the 8 km C-PT (figure 5.4). This is easy to imagine as the upper body and arms mainly produce

the force to generate momentum in double-poling technique (DP). No differences in muscular pain were observed between caffeine or placebo treatment in neither arms nor legs. Other studies have suggested that caffeine lowering pain perception might explain the enhanced performance observed after caffeine ingestion (Doherty & Smith, 2005). Patient studies have also showed an increased performance due to the lowered perception of pain after ingested caffeine (Momsen et al., 2010). Results from the 8 km C-PT conducted by Stadheim et al., (2013) supports the observations of the present study. As with RPE, a TT protocol implies maximal effort, and no differences in muscular pain is not unexpected.

The enhanced performance on the 8 km C-PT is mainly due to an increased speed the first 3 km. Because no differences are observed in perception of pain at these current kilometers in the present study, one cannot conclude the enhanced performance is due to a lowered perception of pain. Despite no differences are observed in RPE throughout the 8 km C-PT, TS performed the test at a higher speed. One could imagine if the TS had performed the 8 km C-PT one more time after caffeine ingestion, and was asked to perform at the same speed as they did during the placebo trial. If RPE and / or pain would have been lowered, one could assume caffeine ingestion prior to a performance task is reducing RPE and / or pain

The questionnaire TS answered both before and after the 8 km C-PT revealed no differences between the treatments on neither form of the day nor motivation. Form of the day scored respectively 69 ± 14 (CAF) and 70 ± 14 (PLA). Motivation was in the same tests 81 ± 11 (CAF) and 80 ± 11 (PLA). This means the TS had a high form of the day and having a very high motivation (Ritchie & Hopkins, 1991). Both these variables potentially would affect RPE and / or perception of pain.

6.4 Lactate

Blood lactate concentration was significantly increased after the 8 km C-PT and more following caffeine ingestions compared to placebo (Table 5.2). These findings are consistent, and one of the most commonly observed effects in many other TT studies (Stadheim et al., 2013; Stadheim et al., 2014; McNaughton et al., 2008; Graham, 2001). Increased amount of circulating adrenaline following caffeine ingestion is one reason researchers suggest as explanation of the increased lactate concentrations (Davis &

Green, 2009). The ability to push harder due to lowered perception of pain is a second reason why one might reach higher lactate concentrations after caffeine ingestions (Davis & Green, 2009). As lactate is a chemical compound used as a marker of anaerobic work, increased concentrations of lactate would indicate higher conducted anaerobic work. This supports the possible enhanced performance following caffeine ingestion.

Adrenaline measurements were performed on three of the TS in this study. Statistically no differences is observed, but magnitude based statistics show a very likely increasing effect on adrenaline due to caffeine ingestion (table 5.2). This likely higher increase is only seen after the 8 km C-PT and not after the incremental test. These findings are consistent with other studies on the topic (Stadheim et al., 2013) It is likely to believe that the observed increase in circulating adrenaline is not alone the reason behind the increased concentrations of blood lactate. However, increased concentrations of adrenaline would directly affect other physiological parameters such as HR (Mazzeo, 2008).

Lactate is continuously produced during glycolysis, and was historically used as a marker of anaerobic utilization during exercise. However, Ingjer, (2008) and Davis & Green (2009) states that higher lactate concentrations might be a result of either performing at a higher intensity or because subjects perform at an intensity above steady state for a longer duration. The theory stating that elevated lactate concentrations might have negative effects on an endurance performance because it working as a marker of anaerobic energy release, is debated.

6.5 Bicarbonate

Blood bicarbonate (HCO_3^-) was significantly lowered after the 8 km C-PT (figure 5.6) and significantly more following caffeine ingestion. Bicarbonate serves as a pH-buffer in the human body as part of the acid-base controlling mechanisms, and works by regulating the excretion of H^+ through pulmonary ventilation (McNaughton et al., 2008). By connecting to H^+ -atoms, bicarbonate forms carbonic acid (H_2CO_3) in which is removed from the body by regular ventilation (H_2O and CO_2). Increased ventilation would therefore decrease the concentration of circulating bicarbonate. Elevated lactate concentrations corresponds to elevated concentrations of H^+ . More bicarbonate is used

in order to prevent the blood of becoming acidic. Peripheral chemoreceptors sense the increased CO_2 concentrations in the blood and increases ventilation.

Caffeine ingestion and exposure to altitude both increases ventilation (Chapman & Mickleborough, 2009). One might imagine the combination having additional effect on ventilation, thus decreasing bicarbonate additionally compared to altitude alone. This might indicate a lowered H^+ -buffering capacity following caffeine ingestion in altitude. Increased circulating H^+ would lower the pH-values, hence towards acidic. After the 8 km C-PT the pH values were significantly lowered compared to placebo (table 5.2). This supports that the bicarbonate H^+ buffering capacity is impaired due to a lower concentration of bicarbonate. Unfortunately no ventilation data were conducted in the present study due to methodical problems.

Importantly, we found that HCO_3^- decreased significantly during the 2-h acclimation after intake of caffeine but not in placebo (figure 5.6). Therefore, subjects were less suited for anaerobic exercise in altitude after caffeine intake compared to placebo. However, subjects started out at a higher speed and reached higher lactate levels after the 8 km C-PT. We also saw that the HCO_3^- decreased to lower level after the 8 km C-PT, indicating that subjects were able to stress their body more by exercise.

6.5 Heart rate

When exercising or competing at high or maximal intensity, one of the most important limiting factors is the total amount of blood being pumped by the heart called cardiac output (Q). Cardiac output is a product of blood volume in one heart stroke (Stroke volume (SV)) and heart rate (HR). As intensity increases, so does Q by increasing HR until near HR_{max} (Bassett & Howley, 2000), and more oxygen is being delivered to the working muscles.

As expected, HR were significantly higher during the 8 km C-PT following caffeine ingestion compared to placebo (figure 5.3). The elevated HR after caffeine ingestion might indicate that caffeine have directly affected HR function and / or allowed the test subjects to exercise closer to their HR_{max} . If one assume SV is constant in caffeine and placebo trial, the increased HR after caffeine ingestion would indicate an elevated VO_2 consumption during the caffeine EP (Stadheim et al., 2013; Stadheim et

al., 2014. As described in the methods, no VO_2 measurements during the 8 km C-PT were conducted due to different methodical problems.

Exposed to altitude, one of the first acute effects together with increased ventilation are increased HR (Engelen, Porszasz, Riley, Wasserman, Maehara & Barstow, 1996). This is immediately only seen during rest and at the same absolute workloads as at lowland. Comparing same relative workloads in altitude and in lowland, no differences are seen in the present study. This also applies for HR_{max} when comparing lowland and altitude. Engelen et al., (1996) suggests the increased HR when exposed to hypoxia may be due to increased amount of circulating catecholamines and / or peripheral reflexes stimulating Q as the arteriovenous (A-V) O_2 content difference decreases. Jensen, Ruge, Lai, Svensson & Eriksson, (2009) have also reported significantly increased HR due to adrenaline infusion.

After the 8 km C-PT increased concentration of circulating adrenaline was observed (table 5.2). Adrenaline increases HR due to sympathetic stimulation (Guyton & Hall, 2011) and as increased concentrations of adrenaline is observed following caffeine ingestion this might be one of the factors contributing to the increased HR (Stadheim et al., 2014). In this study there was not measured any A-V O_2 content difference.

6.7 Submaximal incremental test

During the four submaximal workload of the incremental test, significant increased concentrations of lactate was observed after the three last workloads (workload 2, $p < 0.05$; workload 3 and 4, $p < 0.01$) (Table 5.2). These results are diverse from other studies (McClaran & Wetter, 2007; Stadheim, 2013). However, Gaesser & Rich (1985) observed a small but statistically increase in blood lactate following caffeine ingestions after submaximal workloads. These increased concentrations might indicate that the TS had to work harder to sustain the given intensity and cover more of the need of energy by anaerobic degradation.

Heart rate (HR) did not differ between the treatments during the incremental test. This is consistent with other scientific studies (Stadheim et al., 2013; Stadheim et al., 2014

Interestingly, RPE tends to be lowered following caffeine ingestion and would contradict the suggestion that TS worked harder to obtain intensity during the incremental test. During the submaximal workloads of the incremental test caffeine ingestion resulted in a lowered RPE on the second workload (60% of VO_{2max}) ($p < 0.05$) (Table 5.3). No significant differences were seen on the three other workloads. Despite no significant differences ($p < 0.05$) were conducted, the RPE tended to be lowered following caffeine ingestion on the three other workloads as well ($p < 0.1$). These findings are consistent with Stadheim et al., (2013) findings on the incremental test.

Muscular pain in the arms was also significantly lowered at 2 of the 4 submaximal workloads ($p < 0.05$) (Table 5.3). In addition, muscular pain tended to be lowered at the two other submaximal workloads ($p < 0.1$). This supports the statement that caffeine might lower both RPE and muscular pain when exercising at the same relative submaximal workloads compared to placebo.

6.8 Other influencing factors

There might be other factors beside the mentioned physiological and psychological variables that could explain the probably enhanced performance seen on the 8 km C-PT following caffeine ingestion. A learning effect (Ingjer, 2008) where the TS improve performance from one test to another because they have learned it was taken in to considerations. Stadheim et al., (2013) showed no learning on the same test from test 3 and further on. The first main test was in this study was the fourth time the TS performed the 8 km C-PT. The cross-over design where half of the TS ingested placebo the first test and the other half caffeine, would further ensure valid results.

6.9 Strengths of the study

The present study was conducted in a relevant altitude for athletes (2000 meters above sea-level). This makes the results of this study relevant and athletic-specific to athletes competing in altitude, as few competitions take place in altitude above 2000 meters.

One of the most common approaches to competitions in altitude is to live and train at lowland, and travel up to altitude 2-3 hours prior to the competition, hence acute approach. The 8 km C-PT in this study was conducted after 2 hours of resting at altitude the hypobaric chamber. For athletes using the acute approach to competitions in altitude, the results from the present study would be beneficial.

The present study was conducted in controlled conditions. Food, liquid and training prior to the performance test were all registered. All equipment was always properly calibrated so we know that all measurements are as correct as possible.

As far as the author knows this is the first controlled scientific study who investigated the effect of caffeine ingestion on an endurance performance in relevant altitude for competing athletes.

6.10 Limitations of the study

One limitation of the study is that only 9 test subjects participated in the study. Of these all were male. Since no women participated in the study, we cannot say the results observed in this study would have been the same if any females had participated in the study. The results are on the other hand consistent with other studies using the same protocol (Stadheim et al., 2013; Stadheim et al., 2014), and studies using females as TS (Goldstein et al., 2010). Both Fulco et al., (1994) and Hemmingson & Berglund (1982) reported an increased performance in altitude following caffeine ingestion. Therefore I feel quite sure the results are accurate and trustworthy.

In cross-country skiing there are few competitions where one double-poles 8 km in a row. Additionally one often has other competitors starting in front and / or behind. This will surely affect a performance. This was not present in this study.

Because of methodical difficulties no VO_2 measurement were measured during the 8 km C-PT in the present study. This would obviously be beneficial in order to investigate how physiological parameters are influenced by caffeine ingestion in altitude. To determine if the TS pushed themselves harder following caffeine ingestion would be easier to determine.

6.11 Further prospects and ethical considerations

As previously mentioned, caffeine ingestion is common in many endurance sports and the ergogenic effects are well documented in lowland. In professional endurance sports, the differences between the athletes can be very small. The importance of small enhancing details might be determinant upon which an athlete gets a podium or not. In an athletic perspective it might be important to test caffeine in order to determine if one has an enhancing effect, or not. If one is able to push harder following caffeine ingestion, this

would potentially be dangerous from a health perspective. In 2004 caffeine was removed from WADA's list of forbidden substances and drugs. From 1980 until 2004 urinal caffeine level $> 12 \mu\text{g} \cdot \text{ml}^{-1}$ was considered to be a doping offence. Today caffeine is on the monitoring program of WADA, meaning that an athlete is required to note up use of caffeine, if tested in connection to competition. In the 30 km during the World-cup in Davos (Switzerland, 1560 meters above sea-level) there was a difference of 0.5% from the fifth place and up to the first place. The competition lasted approx. 65 min, and was conducted as a single-start. The ethical aspect of using caffeine ingestion prior to competition is of course the performance enhancing effect. In the present study we found a 1.3 % increase in performance following caffeine. Hypothetically this would change the top 5 list in Davos if some athletes would have used caffeine ingestion, and some not.

Further research on caffeine ingestion in altitude would be beneficial in order to document its influence on endurance performance. Oxygen measurements during an endurance task following caffeine would be interesting to compare to placebo.

7.0 Conclusion

The present study shows that caffeine ingestion is possibly beneficial on an endurance performance in altitude. The improved performance is mainly a result of a higher velocity during the first 3 km of the performance test. The reason for the smaller enhancement of caffeine in altitude compared to studies in lowland might follow difficulties in finding the correct opening-velocity. An increased opening-velocity requires increased anaerobic work. As altitude increases ventilation and the buffering-capacity is lowered, an increase in anaerobic work might result in earlier fatigue compared to lowland. To control the opening-velocity seems to be of vital importance when using caffeine ingestion in altitude.

Furthermore, caffeine ingestion elicited increased heart rate, lactate during the 8 km C-PT. Blood bicarbonate levels were in the same period significantly reduced following caffeine ingestion. All the mentioned parameters would indicate caffeine ingestion made the TS more able to push harder. RPE and muscular pain in both arms and legs did not differ between the treatments during the 8 km C-PT.

8.0 References

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Abbreviations

What	Abbreviations
Arteriovenous	A-V
Caffeine	CAF
Cardiac output	Q
Central Nervous System	CNS
Cross-Country Poling ergometer	CC-POL
Cross-Country Ski Poling Performance Test	C-PT
Double Poling	DP
Endurance Performance	EP
Fatty Free Acids	FFA
Heart Rate	HR
Hypoxic Ventilatory Response	HVR
Phosphofructokinase	PFK
Placebo	PLA
Lactate	La ⁻
Rate of Perceived Exertion	RPE
Standard Deviation	SD
Stroke Volume	SV
Test Subjects	TS
Time to Exhaustion	TTE
Time Trial	TT
The Norwegian School of Sport Sciences	NSSS

APPENDIX

Prosjektbeskrivelse

1.0 Bakgrunn

Koffein har vist å kunne forbedre prestasjonen i flere idretter (Irwin et al., 2011; Ping et al., 2010). Av den grunn er koffein hyppig brukt av idrettsutøvere i konkurransesituasjoner (Goldstein et al., 2010). Mekanismene bak de positive effektene er fortsatt uklare (Stear et al., 2010), men en bedret evne til å arbeide på høyere intensitet etter inntatt koffein er vist (Stadheim, 2011). Dette kan komme av at utøvere kan oppleve mindre trøtthet (Fulco et al., 1994; Stadheim, 2011) og kan oppnå en høyere hjertefrekvens (HF) (Stadheim et al., 2012). I tillegg til å utsette trøtthet (Fulco et al. 1994), kan koffein redusere følelsen av smerte gjennom en økt sekresjon av β -endorfiner (Laurent et al. 2000). Dette kan være faktorer som vil påvirke utgangintensitet og igjen påvirke en prestasjon ved akutt hypoksi. Effekten av koffein på prestasjonsevne i høyden er i mindre grad studert, og resultatene fra de få studiene som er gjennomført er mindre entydige enn de studiene som er gjennomført i lavlandet. Hemmingson & Berglund (1982) var de første til å studere disse variablene da de undersøkte langrennsløpere både i lavland og i høyden (2900 m.o.h.). Inntak av koffein ga økt prestasjon i lavlandet, men ikke i høyden. Fulco et al. (1994) testet effekten av koffein i lavland, ved akutt hypoksi og etter langvarig tilvenning til høyde (4300 m.o.h.). Tilskudd av koffein viste seg å øke prestasjonen både i lavland og ved akutt hypoksi, men viste ikke noen effekt etter langvarig tilvenning i høyden. Når høyden øker, minker partialtrykket for oksygen (PO_2) som følge av redusert barometrisk trykk. Denne tilstanden kalles hypoksi, og kan potensielt føre til O_2 -mangel i blod og muskulatur. En utøvers respons til hypoksi avhenger ikke bare av graden av hypoksi, men også av lengden av eksponering. Derfor blir to typer av hypoksi klassifisert: akutt hypoksi (minutter, timer) og kronisk hypoksi (dager, år) (Wehrin & Hallén, 2006; McArdle, 2006). Ved eksponering for akutt hypoksi reduseres maksimalt oksygenopptak (VO_{2max}). Denne reduksjonen er rapportert allerede fra 580 m.o.h. hos godt trente individer (Gore et al., 1996). Desto høyere høyde man blir eksponert for, desto større er fallet i VO_{2max} (Fulco et al., 1998). Ettersom VO_{2max} er sterkt relatert til prestasjon i de fleste utøvelsesidretter (Bassett & Howley, 2000), kan dette forklare noe av de reduserte prestasjonene man ser i høyde sammenlignet med i lavland. Wehrin & Hallén (2006) fant en reduksjon i VO_{2max} på 4,6-7,5% pr. 1000 meter økning i høydemeter. En reduksjon i VO_{2max} medfører at gitte absolutte belastninger tilsvarer relativt høyere belastninger. Praksis i forkant av konkurranser i høyden er ulik. Noen velger å oppholde seg i høyden i ukene før slike konkurranser, mens andre velger å bo i lavlandet, for så å dra rett opp i høyden og konkurrere (Personlig meddelelse Trond Nystad, Norges Skiforbund). Utøvere som presterer godt i høyden oppgir ofte at de åpner roligere sammenlignet med lavland (Personlig meddelelse, Petter Northug jr). En absolutt lik (HF, VO_2) åpningshastighet i høyde vil resultere i forhøyede blodlaktatverdier (La-bl), og kan potensielt føre til en dårligere prestasjon totalt i en utøvelseskonkurranse.

1.1 Problemstilling

Ettersom dette er et prosjekt som i første rekke er interessant for godt trente konkurransutøvere vil det kommende studiet forsøke å svare på følgende problemstillinger: Kan inntak av koffein ($4,5 \text{ mg} \cdot \text{kg}^{-1}$) øke prestasjonen ved akutt hypoksi (2000 m.o.h.) hos godt trente langrennsløpere?

2.0 Metode

Studien vil gjennomføres gjennom et dobbel-blindet, placebo-kontrollert, cross-over design. Studien vil bli gjennomført i et lavtrykkskammer, hvor forsøkspersonene vil måtte oppholde seg i 2 timer før start av testing. Denne tidsrammen relateres til den tidsrammen som en utøver (som bor lavt, men konkurrerer høyt) bruker i høyden før vedkommende starter å konkurrere.

2.1 Forsøkspersoner

Resultatene fra et slikt prosjekt vil først og fremst ha nytteverdi for utøvere som driver aktivt med utholdenhetsidretter. Forsøkspersonene i dette studiet vil derfor bestå av aktive langrennsløpere i alderen 18-21 år. Studien ønsker å inkludere 10-15 forsøkspersoner. Dette antallet er realistisk å få rekruttert innenfor den spesifikke utøvergruppen vi ønsker. Et slikt antall på 10-15 FP gir den statistiske styrken vi trenger for at datamaterialet skal kunne ha en statistisk styrke på rundt 80%. Den statistiske styrken i studien er beregnet ut fra spredning i andre studier hvor en koffein dosering på 3-6 mg $\text{mg} \cdot \text{kg}^{-1}$ er gitt. Disse studiene viser en forbedring i konkurranse-tester på 3-5% (Bruke, 2008). Standardavviket i de samme studiene ligger i området 3-4. Ved å bruke GraphPad StatMate 2.00, velge parret T-test og sette standardavviket til 4, viser beregninger at man trenger 12 FP for å kunne få en forventet forbedring på 3%, om den statistiske styrken skal være 80%. Siden den kan forventes en drop-out på 20%, velger vi derfor å ha minst 15 FP ved start av studiet. Forsøkspersonene vil bli grundig informert om alle aspekter vedrørende prosjektet før de eventuelt gir sitt skriftlige samtykke om deltakelse.

2.2 Test-protokoll

Testene vil bli gjennomført i perioden september – oktober på laboratoriet ved Norges idrettshøyskole (NIH).

2.2.1 Pre-test

Forsøkspersonene vil gjennomføre to separate pre-tester. Disse pre-testene vil virke som tilvenning, samt danne grunnlaget for beregning av arbeidsbelastning med tanke på hovedtestene. Beregningene gjøres på bakgrunn av VO₂max-tester gjennomført på de to dagene med pre-tester.

2.2.2 Hovedtest

Forsøkspersonene vil gjennomføre 2 hovedtester. En hvor FP blir gitt koffein og en hvor det blir gitt placebo. Hvilken rekkefølge hovedtestene gjennomføres i vil bli randomisert for hver enkelt FP. Forsøkspersonene (FP) vil uansett type hovedtest oralt innta 4,5 mg $\text{mg} \cdot \text{kg}^{-1}$ koffein eller placebo utblandet i sukkerfri saft (Fun Light) for å kamuflere den distingte smaken koffein har. Inntaket av koffein vil skje 1 time før start av hovedtestene (2 timer etter utøverene har gått inn i trykkammeret). Hovedtestene gjennomføres som en standard trappetest og en avsluttende prestasjonstest. I trappetesten vil FP gjennomføre 4 belastningstrinn (à 5 minutter), med 1 minutt pause mellom hvert belastningstrinn. De siste 2,5 minuttene vil danne grunnlaget for beregning av steady-state verdier for VO₂ og HF. Målinger av blodlaktat La^- vil bli tatt før testen, i hver pause, samt etter testen (Fig 2). Arbeidsbelastningen på de ulike trinnene vil være henholdsvis 55%, 60%, 65% og 70% av de individuelle VO₂max-verdiene. Denne trappetesten vil også fungere som oppvarming.

Prestasjonstesten gjennomføres som en 8 km staketest. VO₂ og HF vil bli registrert under hele prestasjonstesten. Blodlaktat [La-bl] vil bli tatt rett før, og rett etter testen. Det vil bli tatt veneprobe før inntak av placebo/koffein og rett før/rett etter prestasjonstestene for analyse av hormoner, metabolitter og myokiner. Prøvene vil bli oppbevart i biobank etter gjeldende regler.

2.3 Mat og drikke i forkant av testene

Forsøkspersonene vil fritt kunne velge å spise og drikke hva de vil i dagene før hovedtestene. Det er likevel restriksjoner på inntak av koffein og alkoholholdige produkter. I tillegg ønsker en at forsøkspersonene spiser som de ville ha gjort innfor en normal langrennskonkurranse. De siste to timene før hovedtestene starter vil forsøkspersonene ikke få anledning til å innta mat eller drikke som inneholder næringsstoffer. For å kontrollere at forsøkspersonene har det samme næringsinntaket 24 timer i forkant av begge hovedtestene vil det bli delt ut et kostholdsskjema. Her vil FP

også måtte registrere hva de har trent de siste 48 timene før testen. Hard trening vil ikke være tillatt i dette tidsrommet. Forsøkspersonene er anbefalt å avstå / ha et lavt inntak av koffein de siste 48 timene før test ($\leq 100\text{mg}$). Dette gjøres for å sikre en størst mulig effekt av koffein under testene (Graham, 2001). På testdagene har forsøkspersonene ikke lov til å innta annen koffein enn den de eventuelt får av forsøksleder.

3.0 Databehandling

All behandling av data fra studiet vil bli gjennomført gjennom de statistiske programmene Statistical Package for the Social Sciences (SPSS) versjon 18 og Microsoft Excel (Windows Home 2010). bli benyttet for å undersøke eventuelle forskjeller mellom gruppene. Alle data vil bli presentert som gjennomsnitt \pm standardavvik. Effekten av koffein på prestasjonsevnen vil bli analysert ved en parret T-test. Signifikansnivået er satt til $p < 0,05$.

4.0 Ethiske aspekter

Som i alle andre former for trening og testing, vil det også her være en risiko for skader. Øvelsene som skal gjennomføres i dette prosjektet er forholdsvis enkle, og risiko for skader regnes derfor som lav.

Ved et oralt inntak av koffein i en størrelsesorden på $4,5 \text{ mg} \cdot \text{kg}^{-1}$ vil normalt føre til en fysiologisk konsentrasjon av koffein i plasma mellom 20-35 $\mu\text{mol/L}$ (Graham, 2001). Denne mengden koffein vil tilsvare rundt 4 kopper svart kaffe eller 3,5 bokser med Red Bull (Burke & Green, 2009). Selv om det er rapportert om smerter i mageregionen (Graham, 2001), blir de helsemessige risikoene med en slik dose koffein regnet som svært lave (Graham, 2001; Bruke & Green, 2009). Ganio et al. (2009) benyttet større doseringer av koffein ($9-12 \text{ mg} \cdot \text{kg}^{-1}$) og fant ingen økt risiko for forhøyet HF, irritabilitet eller rastløshet hos FP som følge av slike høye doser. Det virker som at det eksisterer individuelle forskjeller hva gjelder bivirkninger av inntatt koffein. Tidligere studier ved NIH har ikke rapportert om noen bivirkninger ved samme koffeinkonsentrasjon. Studiet vil gjennomføres i henhold til bestemmelsene i Helsinkideklarasjonen. Søknad om gjennomføring av prosjektet vil sendes til den regionale etiske komité (REK) så snart foreliggende prosjektplan godkjennes. Alle forsøkspersoner vil bli bedt om å fylle ut et standardisert helseskjema før de kan bli med i studien. Et av spørsmålene går ut på om FP tidligere har opplevd ubehag ved inntak av koffeinholdige drikker. Hvis FP svarer ja på ett eller flere av spørsmålene i helseskjemaet, vil de bli undersøkt av lege, og få

gjennomført EKG-undersøkelse før de eventuelt kan delta i studien. Alle forsøkspersonene vil bli skriftlig informert om studiet, og de kan når som helt trekke seg uten å måtte oppgi grunn, og uten at det vil gi videre konsekvenser. Alle data vil bli behandlet konfidensielt ved å gi hver FP et egen kodenummer. Kun prosjektledere vil ha mulighet til å identifisere den enkelte FP på bakgrunn av dette kodenummeret.

5.0 Organisering

Studien vil bli gjennomført av Eirik Myhr Nossun og Hans Kristian Stadheim fra Norges Idrettshøyskole ved seksjon for fysisk prestasjonsevne. Hovedveileder vil være professor Jørgen Jensen. Stadheim er også biveileder for Eirik Myhr Nossun sin masteroppgave.

6.0 Finansiering

Studien er et mastergradsstudie og vil bli finansiert gjennom budsjettet til Seksjon for Fysisk Prestasjonsevne ved Norges Idrettshøyskole.

How is your form of the day / motivation?

100	Perfectly
95	Very very well
90	Very very well
85	Very well
80	Very well
75	Very well
70	Well
65	Well
60	Well
55	Moderately
50	Moderately
45	Moderately
40	Poorly
35	Poorly
30	Poorly
25	Very Poorly
20	Very Poorly
15	Very Poorly
10	Very Very Poorly
5	Very Very Poorly
0	Terribly

Ritchie, S. E & Hopkins, W. G. (1991) The intensity of exercise in deep-water running.
Int.J.Sports.Med, 12, 27-29

