PREVALENCE AND BLOOD PROFILE ANALYSIS OF SOUTH AFRICAN GOLD- MINERS WORKING UNDERGROUND WHO PRESENT WITH EXERCISE-ASSOCIATED MUSCLE CRAMPS AT WORK

by

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DECLARATION

I, Dr Rudolph De Wet, hereby declare that the work on which this dissertation is based, is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part of it has been, is being, or has to be submitted for another degree in this or any other University.

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It is being submitted for the degree of Master's in Sports and Exercise Medicine in the School of Medicine in the Faculty of Health Sciences of the University of the Free State, Bloemfontein.

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CONFLICT OF INTEREST

The author states no conflict of interest.

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ABSTRACT

Background:

Almost a hundred years after the first reports on the possible aetiology of muscle cramping in mine workers, the debate on the mechanism and contributing factors to the development of cramping rages on and we are no closer to preventing cramping. The current theories of the "Electrolyte depletion and Dehydration model" or "Salty Sweat" with the addition of fatigue (Bergeron, 2003; Eichner, 2007; Armstrong, *et al.*, 2007) and the current, and more accepted "Altered Neuromuscular Control" hypotheses (Schwellnus, 2008) are still polarising the debate surrounding EAMC.

Aims:

The aim of this study was not to prove or disprove any of the current theories surrounding EAMC. This study's aims were to describe the prevalence and certain environmental, biochemical and haematological variables in gold miners working underground who presented with exercise-associated muscle cramps (EAMC) at work. It further aimed to formulate or describe the 'normal' profile of haematological and biochemical changes during a shift, in the mining population. This "normal" control data were also generated to assist in the interpretation of the haematological and biochemical variables from the group who presented with EAMC.

Methods:

This study consisted of two parts: Part 1 was a retrospective descriptive study of the blood profiles of underground mine workers who presented with EAMC, together with biological factors relating to these workers. The procedure for data collection for the cramp group was to extract routine data from the clinical notes of miners who presented to the medical stations with EAMC. Part 2 was a prospective study consisting of a collection of blood-samples, before and after an 8 hour shift (2 hours commuting and 6 hours of physical labour), on a volunteer group of healthy underground mine workers not presenting with cramps. The data were sent for statistical analyses. Due to the exploratory nature of this study, descriptive statistics were primarily used to report the findings. Trends were observed and expanded on based on available literature and specialist consultation.

Results:

Due to the large amount of data generated by the study, the discussion of the results was presented under four main category headings. These categories were chosen following a literature review and specialist consultation on the significant findings from the study. These categories were hydration and electrolyte disturbances, muscle damage, muscle fatigue and inflammation.

The "normal" or control participants were well to slightly over hydrated individuals, with progressive muscle injury (increased CK levels, but no increase in myoglobin) during a working week. The participants experience muscle fatigue with a slight WCC reaction as a result of his daily labours. The individual mostly worked in cramped spaces with heavy and sometimes vibrating tools or walked long distances or stood for long periods of time. They were also able to regulate their body temperature and homeostasis with minimal stress on their liver and kidneys.

The participants who presented with EAMC mainly performed heavy physical labour but there were also the group that remained in cramped positions for prolonged periods. They showed possible signs of dehydration, muscle fatigue, muscle damage (raised myoglobin and CK levels), and inflammation.

Conclusion:

There seems to be an unnecessary polarisation between those for and those against the inclusion of electrolyte and dehydration into the aetiology of EAMC. One of the main arguments against the inclusion of these hypotheses (electrolyte & dehydration) is that the proponents basically fail to link how a systemic abnormality may cause a local disruption in homeostasis. This is a sound argument if we consider electrolyte disturbances and dehydration to be the sole cause of cramping. One should rather see this as part of a collective subset of contributing factors that each add to priming the body's muscles for developing cramps. Single or groups of muscles that do then cramp are being triggered to cramp in the "primed" environment by factors such as fatigue.

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LIST OF ABBREVIATIONS

ALP:	**Alkaline Phosphatase**
ALT:	**Alanine Aminotransferase**
AST:	**Aspartate Aminotransferase**
BMI:	**Body Mass Index**
Ca:	**Calcium**
CK:	**Creatine Kinase**
Cl:	**Chloride**
CO_2:	**Carbon dioxide**
CON:	**Control group**
$CON_{(post)}$:	**Control group post-shift values**
$CON_{(pre)}$:	**Control group pre-shift values**
CRA:	**Cramp group values**
EAMC:	**Exercise-associated muscle Cramps**
GFR:	**Glomerular Filtration Rate**
GGT:	**Gamma Glutamyl transferase**
Hb:	**Haemoglobin**
Hct:	**Haematocrit**
K:	**Potassium**
MDRD:	**Modification of Diet in Renal Disease**
Mg:	**Magnesium**
MOPD:	**Medical out-patient department**
Na:	**Sodium**
Ph:	**Phosphate**
SD:	**Standard Deviation**
U&E (Creat):	**Urea, Electrolytes and Creatinine**
U/I:	**Units International**
UFS:	**University of the Free State**
WCC:	**White Cell Count**

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Almost a hundred years after the first reports on the possible etiology of muscle cramping in mine workers (Edsall, 1908; Oswald, 1925; Brockbank, 1929; Derrick, 1934; Talbott, *et al.*, 1933; Talbott, 1935) the debate on the mechanism and contributing factors to the development of cramping rages on and we are no closer to preventing cramping. The current theories of the "Electrolyte depletion and Dehydration model" or "Salty Sweat" with the addition of fatigue (Bergeron, 2003; Eichner, 2007; Armstrong, *et al.*, 2007) and the current, and more accepted "Altered Neuromuscular Control" hypotheses (Schwellnus, 2008) are still polarising the debate surrounding EAMC.

The design of the study consisted of two parts. The first part was a retrospective descriptive study of information gathered routinely at the involved mine on patients that presented with EAMC. This information gathered routinely included physical symptoms, environmental and occupational information as well as a comprehensive blood panel. The second part was a prospective collection of blood-samples before and after a shift on a volunteer group of workers to explore the "normal" physiological changes and adaptations during a shift of manual physical labour in the underground environment of a gold mine in South Africa.

The participants in the first part of the study, who presented with EAMC were mine workers working underground in one of the South African gold mines that presented to the medical services with muscle cramps during or within 24h following a work shift. The second group of participants was mine workers working underground in one of the South African gold mines that present voluntarily for participation in the study. In the group that presented with cramps (CRA), bloods and other data were collected after they presented with their cramping episode as per the companies normal protocol. The second or control group (CON) had bloods and data collected both directly before the shift and immediately after the same shift. The data were collected and then sent to the biostatistics department for processing. The processed data were then examined for prevailing trends and presented according to these observed trends in this study.

The notion Exercise-Associated Muscle Cramps (EAMC) is defined as "painful, spasmodic and involuntary contraction of skeletal muscle that occurs during or immediately after exercise" (Schwellnus, *et al.*, 1997). The use of the term EAMC was felt to be justified in this group of participants as all of the muscle cramping incidents occurred during physical activity (exercise).

1.2 GOALS

The goal of the research was to describe the association of the identified factors from the data collected with EAMC. Special attention was also given to observations made, which could aid in areas of speculative hypotheses for which sufficient scientific data are lacking.

1.3 AIMS

This study will not aim to prove or disprove any one of the current two hypotheses regarding EAMC, instead it will merely aim to describe the prevalence and certain environmental, biochemical and haematological variables in gold miners working underground who present with exercise-associated muscle cramps (EAMC) at work.

It will further seek to formulate or describe the 'normal' profile of haematological and biochemical changes during a shift, in the mining population. These "normal" or expected changes or physiological responses in a mine worker when performing his or her physical duties in the underground environment will then be compared to the findings in the population that presented with EAMC. Trends and observations will then be presented.

CHAPTER 2

LITERATURE STUDY

2.1 INTRODUCTION

Mine-workers presenting with cramping are often spot-diagnosed with heat-related illness and not Exercise-associated Muscle Cramping (EAMC). The definition of EAMC is a "painful, spasmodic, involuntary contraction of skeletal muscle that occurs during or immediately after exercise" (Schwellnus, *et al*., 1997) and seeing as to how the patients mainly presented with cramping whilst performing physical labour, it is felt that the use of the term EAMC is justified. The main and initial criterion for inclusion into the CRA group of the study was the presence of cramping. All of the individuals included in the CRA group thus had an episode of cramping during or within hours following a work shift. The study describes haematological, biochemical, and environmental findings collected in patients that presented with cramps whilst performing physical labour / exercise underground. Chapter 2 describes the current controversies in the literature regarding EAMC. Information on some relevant mining-specific issues that are required to interpret the data is also provided.

2.2 CURRENT DEBATE REGARDING EAMC

Exercise-associated muscle cramps (EAMC) is widely researched and described throughout the scientific literature. The current accepted pathophysiological basis for cramps is an abnormality of muscle relaxation (Schwellnus, 2009). However, consensus regarding the cause behind this abnormality has not yet been achieved. Currently, two main schools of thought on the aetiology of EAMC exist, namely:

i. "Electrolyte depletion and Dehydration model" or "Salty Sweat" hypothesis (Bergeron, 2003); and the
ii. "Altered Neuromuscular Control" hypotheses (Schwellnus, *et al.,* 1997).

2.2.1 "Electrolyte depletion and dehydration" hypothesis

The "Electrolyte depletion and dehydration" hypothesis was initially founded on anecdotal evidence and smaller studies (Edsal, 1908; Talbot, 1935). The "Electrolyte depletion and dehydration" hypothesis proposed that muscle cramps resulted from an increase in the sweat sodium content resulting in sodium depletion, as shown in Figure 2.1 (Bergeron, 2008; Eichner, 2007; Stofan, *et al.*, 2005). To support their hypothesis, in the face of mounting evidence opposing their theory, the so-called 'Triad' of depleted electrolytes, dehydration and the recently added muscle fatigue was suggested (Armstrong, *et al.*, 2007; Eichner, 2007). Muscle fatigue was added in an attempt to compensate for the fact that this hypothesis offers no explanation for the pathophysiological mechanism of EAMC and effectiveness of rest and passive stretching in the relief of acutely cramping muscles (Armstrong, *et al.*, 2007; Eichner, 2007).

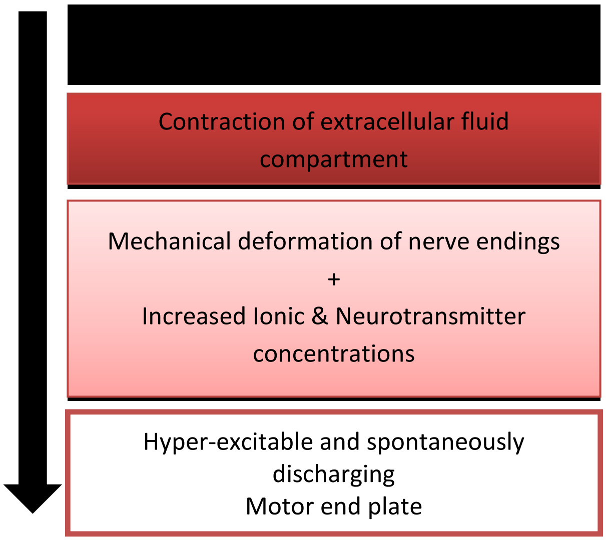

FIGURE 2.1: THE POSTULATED PATHOPHYSIOLOGICAL MECHANISM AS PER THE "ELECTROLYTE DEPLETION AND DEHYDRATION" HYPOTHESIS (BERGERON, 2003)

No evidence was presented to support the proposed pathophysiological basis for the electrolyte depletion and dehydration hypothesis. Electrolyte disturbances that have been highlighted by studies as a cause or predisposing factors are hypochloraemia (Edsall, 1908; Oswald, 1925 in Schwellnus, 2008), hyperkalaemia, hypomagnesaemia and hypocalcaemia (Brockbank, 1929; Derrick, 1934; Talbott, *et al.*, 1933; Talbott, 1935 in Schwellnus, 2008).

2.2.2 "Altered Neuromuscular Control" hypothesis

The "Electrolyte depletion and dehydration" hypothesis was disputed or challenged by a cohort study that disproved the relation between EAMC and altered electrolyte concentrations (Schwellnus, *et al.,* 2004). According to the "Altered Neuromuscular Control" hypothesis and its close association to muscle fatigue, the pathophysiology of EAMC involves an increase in Alpha 1 motor-neuron activity combined with a decreased inhibitory reflex from the Golgi Tendon Organ (GTO) (Talbott, 1935). Fatigue plays a vital role in this hypothesis. Fatigue is thought to alter peripheral muscle receptors, increasing the firing rate of muscle spindle Type Ia and II afferents. The GTO also shows a decrease in Type 1b afferent activity associated with muscle fatigue. As stretching of an actively cramping muscle is the universally acceptable management (Schwellnus, *et al.,* 1997), it is thought that the resultant stress on the Golgi tendon results in a reflex inhibitory effect on the Alpha 1 motor-neuron (Schwellnus, *et al.*, 1997).

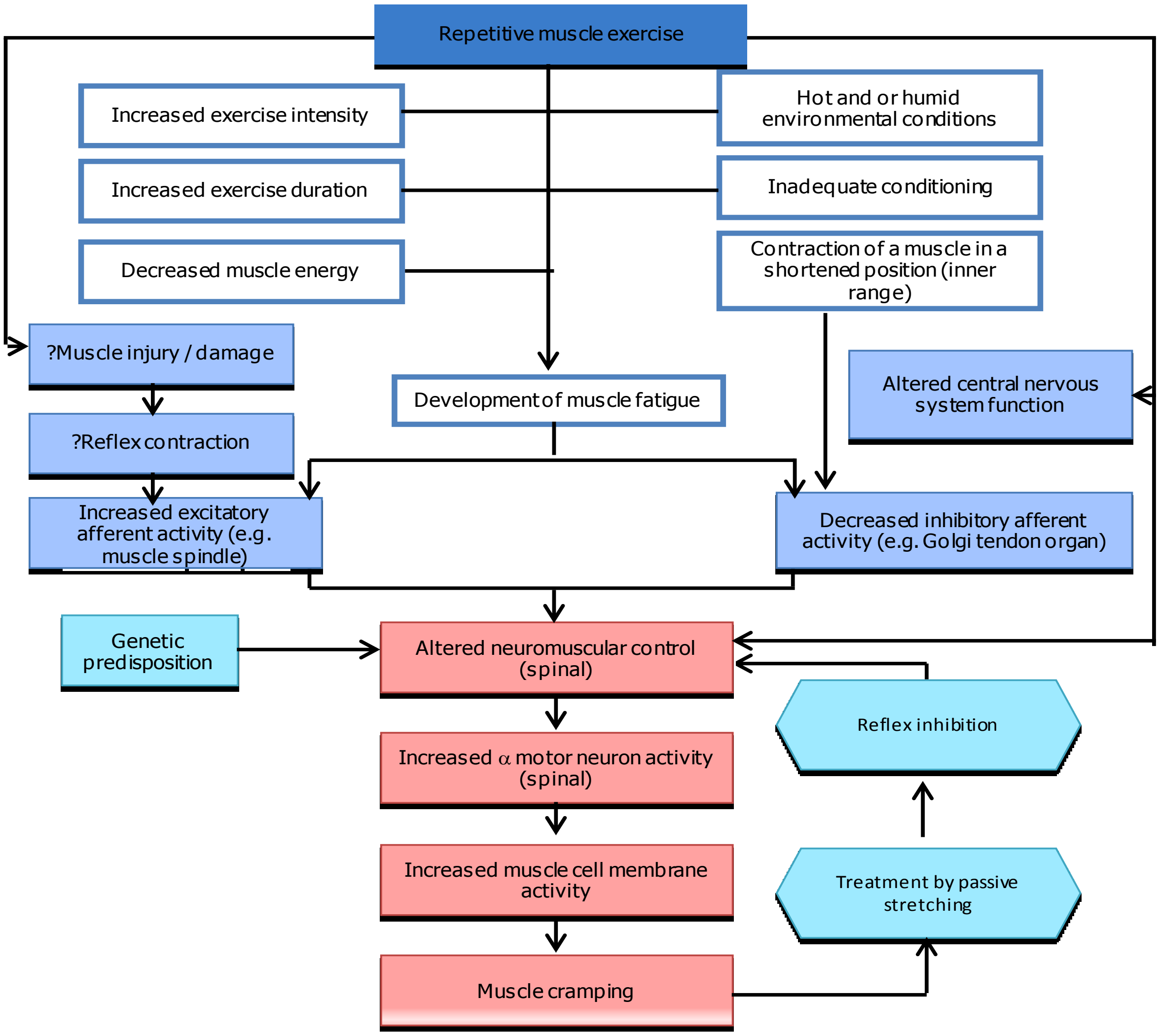

FIGURE 2.2: ALTERED NEUROMUSCULAR CONTROL – EXPLANATION OF THE PATHOPHYSIOLOGY OF EAMC. ADAPTED FROM SCHWELLNUS (2009)

The "Altered Neuromuscular Control" hypothesis is depicted in Figure 2.2 (Schwellnus, 2009). From Figure 2.2 it can also be seen that the progression, from repetitive muscle contractions to muscle fatigue, is influenced by various factors (increased exercise intensity or duration, inadequate conditioning, etc.). These influences or factors and their contributory roles in the pathophysiology of EAMC are still unclear.

2.3 CURRENT KNOWLEDGE REGARDING POSSIBLE FACTORS ASSOCIATED WITH EAMC

This section summarises the current knowledge on factors possibly associated with the development of EAMC.

2.3.1 Hydration and Electrolytes

2.3.1.1 *Hydration*

The dehydration hypothesis of EAMC originates from observations in early case reports of labourers (Edsall, 1908; Talbot, 1935). The arguments against these studies are amongst others that in none of these anecdotal accounts was hydration status actually documented, no control groups were included and study measurements were not done at the time EAMC occurred (Bergeron, 2003 ; Eichner, 2007). An attempt was thus made in this study to address these factors.

In a study by Shearer (1990), blood was taken for estimation of serum sodium, potassium, magnesium, calcium, inorganic phosphate, and serum total protein from 50 underground and 52 surface workers for a comparison. He also had a third group of 55 participants that presented with heat illness. These 55 participants that presented with heat illness had blood drawn for electrolytes and protein with haematocrit (Hct) on day zero (day of the heat illness incident), one, two and seven. The patients that presented with heat illness (37 of 55 whose main presenting symptom was cramps) presented with a haemoconcentration and plasma volume reduction on day 0 (incident date) that consistently improved until day 7. The changes in serum total protein were used as an estimate of the degree of haemoconcentration and serum electrolyte levels was adjusted accordingly (Ohira, *et al.,* 1977). The rationale for using the simpler method of changes in serum total protein to correct electrolyte values, rather than the more commonly used method using haemoglobin (Hb) and haematocrit (Hct) changes (Dill & Costill, 1974), is that changes in serum protein have been found to match changes in haematocrit during exercise in heat (Senay & Kok, 1977). In contrast, Myhre and Robinson (1977) found that total circulating protein remains constant in dehydration, and it provides a reasonably accurate estimate of the magnitude of plasma volume changes (Myhre & Robinson, 1977).

Dialysis is an extreme example of plasma volume and electrolyte shifts. It could highlight some factors that may occur more subtly in athletes and labourers, but play an important contributory role in cramping. Muscle cramps are a common complication during dialysis. Earlier literature postulated that muscle cramping in patients being dialysed are caused by plasma or muscle cell hypo-osmolality as well as a rapid plasma volume decrease as seen when dialysis patients fluid overloaded themselves by ingesting large amounts of fluids prior to dialysis (Jenkins & Dreher, 1975). This larger plasma volume is then reduced rapidly during dialysis, resulting in cramping (especially of the leg muscles). This hypothesis was based on findings where an infusion of a bolus of hypertonic saline relieved the cramping in dialysis patients. This may suggest that it is the faster rate of fluid loss that is important in cramping and not gradual fluid loss in acclimatised patients (Jenkins & Dreher, 1975). The author, however, acknowledges that this cramping phenomena (in dialysis patients) is not exercise-associated (i.e. does not occur during or immediately after exercise) and may have a different pathogenesis.

2.3.1.2 ***Electrolytes***

The study by Shearer (1990) showed that when you correct for haemoconcentration (dehydration) using either of the two described methods, serum total protein (Ohira, *et al.*, 1977) or Hb / Hct (Dill & Costill 1974) you have a very hyponatraemic or sodium depleted (mean of 105.6mmol.L^{-1}) picture of patients presenting with cramps. This is compared to the relatively constant uncorrected sodium values in the same patients presenting with cramps with a mean average of 134mmol.L^{-1}.

Higher fluid intake was also associated with lower corrected sodium (Na) levels (dilutational hyponatremia). The corrected values at day zero (incident day) saw decreased electrolyte concentrations in sodium (21%) and potassium (25%), with calcium (6%) and phosphate (5%) when compared to day seven post-incident. Magnesium, however, was 13% higher on day zero (incident date) than on day seven post-incident indicating that there was a higher corrected serum concentration of magnesium on the incident day. In his study, Shearer (1990) found the following changes in serum magnesium (Mg), calcium (Ca) and phosphate (Ph):

Uncorrected Mg level was considerably higher than the control group or the corrected Mg level via the protein corrected method. The uncorrected Mg level was even higher when compared to the corrected magnesium using the Hb/Hct method, which was similar to the control group level on day zero. Other studies that did not have a cramp group, and only looked at the changes in serum magnesium (uncorrected) in marathon runners (Cohen & Zimmerman, 1978; Refsum, *et al.,* 1973) and after exercise in the heat (Wolfswinkel, *et al*., 1980) showed decreased levels of magnesium.

In the study by Shearer (1990), uncorrected Ca on day zero was considerably higher than the corrected Ca levels, again more so when using the Hb/Hct corrected method. In contrast, the control group levels were less than the uncorrected but more than corrected Ca levels. Hypocalcaemia has also been suggested to be secondary to the alkalosis of hyperventilation, which is commonly found in extreme heat exposure (Lampetro, 1963; Sprung, *et al.,* 1980). The hyperventilation associated with exercise alone was not pertinently mentioned in the aforementioned studies or other studies that could be found.

Phosphate followed a very similar pattern to calcium explained above. Phosphate also has been found to be raised in heat exhaustion (Leithead & Lind, 1964) and lowered in heat stroke (Sprung, *et al*., 1980).

The above elements, corrected and uncorrected, returned to approximately "normal" (control group levels) at day 7 (Shearer, 1990).

<u>CO2</u>

Serum carbon dioxide level (CO_2) is measured instead of bicarbonate. The total CO_2 content includes the serum bicarbonate plus other available forms of carbon dioxide (dissolved CO_2 and carbonic acid). Generally, as much as 95% of the serum bicarbonate is made up by the total CO_2 content, thus we can use this measurement as an excellent estimator of serum bicarbonate (Centor, 1990).

2.3.2 Muscle damage or breakdown

Cramping often accompanies, or is an early sign or symptom of rhabdomyolysis (Anzalone, *et al.*, 2010; Clarkson & Sayers, 1999; Cleary, *et al.,* 2007; Moeckel-Cole & Clarkson, 2009). Rhabdomyolysis again is often a complication of strenuous physical exertion and as such there seems to be a link or at the least an association between strenuous exercise / physical exertion, rhabdomyolysis and cramping. This is the motivation for the inclusion of point 2.3.2, concerning factors influencing rhabdomyolysis below in the discussion surrounding EAMC.

2.3.2.1 *Strenuous exercise*

Rhabdomyolysis is a relatively common complication of strenuous exercise, as evidenced by the military recruit data (Olerud, *et al.,* 1976) and the large number of reports of "white collar rhabdomyolysis" gathered by Knochel (1990). Knochel (1990) had termed exercise-induced rhabdomyolysis "white collar rhabdomyolysis" because of its high incidence in intelligent, well-educated professionals who can arrange their work schedules to allow for daily running. Interestingly, in exercise-induced rhabdomyolysis in professional athletes, neither the amount of exercise nor the level of training appears to be a reliable predictor for the development of rhabdomyolysis (Senert, *et al.,* 1994). Furthermore, they found that exercise-induced rhabdomyolysis without complicating nephrotoxic cofactors has a significantly lower incidence of acute renal failure compared to other forms of rhabdomyolysis, this being true even with an average creatine kinase (CK) level of 4047 ± 3429 $U.L^{-1}$ on admission to hospital.

2.3.2.2 *Prolonged exercise*

In a study tracking muscle injury and white cell response in 1987 during a 16 hour march, Galun (1987) found a parallel increase in plasma creatine kinase activity from 127 ± 4.4 $u.L^{-1}$ to 539 ± 106.3 $u.L^{-1}$ ($P< 0.001$), indicating muscle cell damage and also an accompanying increase in serum white cell count (WCC) (see below) (Galun, *et al.,* 1987).

2.3.3 Muscle fatigue

Muscle fatigue has been discussed in Section 2.2.2. The "Altered Neuromuscular Control" hypothesis has been supported by a number of high quality studies, and answers or explains some of the pitfalls accompanying the "Dehydration and Electrolyte depletion" hypothesis; for example, the effectiveness of passive stretching as a management of acute cramping and the localised nature of EAMC (Schwellnus, 2009).

The administration of a carbohydrate containing solution showed a delay in the onset of EAMC (Jung, *et al.,* 2005). This supports a nutritional priming or contributory etiological factor in the development of EAMC. Carbohydrate supplementation could be delaying the depletion of muscle glycogen stores, and thus fatigue that leads to EAMC. Studies to measure the actual decline of glycogen stores in exercising skeletal muscle have not been undertaken yet as this would require muscle biopsies on the athletes (Jung, *et al*., 2005).

In the mining sector, since the advent of formal acclimatisation strategy, there has been a greatly decreased incidence of heat stroke and related episodes of cramping. This would indicate that, reducing the fatigability of muscles and aiding in a gradual exposure to the combination of physical exertion in adverse environmental conditions (heat & humidity), by acclimatisation exercises, helps reduce the incidence of cramping and heat-related illnesses (Strydom, *et al*., 1975).

2.3.4 Inflammatory response

Galun (1987) indicated that muscle cell damage was accompanied by an increase in WCC (Galun *et al*., 1987). As mentioned above, muscle cell damage (exertional rhabdomyolysis) often presents with cramping following exercise (see EAMC definition above [Scwellnuss, 2009]) (Anzalone, *et al.,* 2010 ; Clarkson & Sayers, 1999 ; Cleary, *et al*., 2007; Moeckel-Cole & Clarkson, 2009).

2.3.4.1 *Effect of exercise, hydration status and temperature on the immune system*

Moderate exercise has been shown to enhance immune function whereas prolonged or intense exercise has shown immunosuppressive results (Gleeson, *et al.*, 2004; Nieman, 1994; Pedersen & Hoffman-Goetz, 2000). One mechanism for immunosuppression during prolonged or intense exercise is the exercise-induced elevation in plasma cortisol. Cortisol is a glucocorticoid released from the adrenal cortex in response to stress. Cortisol has immunosuppressive and anti-inflammatory effects, acting to mediate the recovery from immune activation early in the stress response, thus preventing an "overshoot" of the immune reaction (Mitchell, *et al.*, 2002; Sorrells & Sapolsky, 2007; Tønnesen, *et al.* 1987; Walsh & Whitham, 2006).

Interestingly, previous studies found that dehydration also leads to an increase in cortisol levels in the blood (Francesconi, *et al.*, 1985; Francis, 1979).

2.3.4.2 *Exercise and temperature effect*

McFarlin and Mitchell (2003) investigated the effects of similar type and duration of exercise in heat (38°C) and cold (8°C) by the same group of participants and its effect on the immune system. It was found that skin and core temperature were significantly lower when exercising in the cold than in the heat ($p < 0.05$). The average total leukocyte count (WCC) was greater immediately after (40%) and 2 h (74%) after the exercise bout, than the count prior to exercise and 24h after the exercise bout in both the hot and cold group ($p < 0.05$). The neutrophil count was greater immediately after (49%) and 2 h (132%) after the bout than the count prior to exercise and 24 h after in both the hot and cold group ($p < 0.05$). Lymphocyte count was greater immediately after exercise (24%) in the hot group compared to the cold group ($p < 0.05$). Exercise in the hot group caused significant increases for skin and core temperatures above those observed in the cold group ($p < 0.05$). The Physiologic Strain Index (PSI) was also greater in the hot than in the cold group (McFarlin & Mitchell, 2003).

2.3.4.3 *Cell type response*

Duration of exercise

Leukocytosis and neutrophil activation accompany short- (even within two hours of exercising (Biondi, *et al*., 2003)) and medium-length exercise, while further studies have shown this especially during and following prolonged exercise (Biondi, *et al*., 2003). The effect of exercise on the WCC with medium and prolonged exercise in 40, 60 and 120km marches were examined. The leukocytes level escalated from the pre-march level midway during the exercise to $11.3 \pm 0.8 \times 10^9.L^{-1}$ and then reduced to below the pre-march level one hour after the march $7.1 \pm 0.9 \times 10^9.L^{-1}$. The WCC again normalised by the following morning $8.5 \pm 0.3 \times 10^9.L^{-1}$. These marches were performed in a warm environment. These studies suggest WBC counts return to baseline values before exercise is terminated. This phenomenon possibly reflects WCC infiltration to damaged muscle tissue (Galun, *et al.,* 1987) (cf. on accompanying CK values).

Intensity of exercise

When compared to the above longer duration of exercise at somewhat lower VO_2Max, shorter more intense exercise (short- (1.7 km), middle- (4.8 km) and long- (10.5 km)) ran at a speeds close to VO_2Max, showed a prompt mobilisation of white cells, and lymphocytes in particular, following the exercise (Hansen, *et al*. 2001). The initial increase in the number of lymphocytes is succeeded by a significant decrease in lymphocytes leading to lymphopenia (Hansen, *et al.* 2001). In the study by Hansen (2001) lymphocyte levels decreased 61-68% following intensive exercise compared to the pre-exercise values in all 3 groups. This study also showed a close correlation between the initial increase in plasma cortisol concentration after exercise and the subsequent lymphopenia. There was also delayed but significant neutrophil granulocytosis noted in all subjects, reaching a peak between two and four hours after the exercise.

Repetitive bouts of exercise

In a small study by McFarlin, *et al.* (2003) they show data suggesting that two bouts of endurance exercise in 1 day produce an cumulative effect for total leukocyte and neutrophil counts and to a lesser degree lymphocyte counts, but did not appear to impact shifts in natural killer cells concentration. This was further supported by a study by

Bøyum, *et al.* (2002) who also found that the total oxidative potential of polymorphonuclear neutrophil (PMN) in blood remains at a higher level with short intervals between exercise bouts (i.e. three hours instead of six hours), possibly due to a combined effect of cell number increase and the priming state of PMN. This may suggest that for intensive training twice a day, a recovery phase of five to six hours is preferable. They suggested that an elevation in cell number was best explained by a combined effect of catecholamines and cortisol during exercise.

When considering the effect of exercise on WCC, as seen from the above mentioned studies as well, there is a known neutrophilia that develops. The question is whether the cell functions are altered as well as whether the adaptability of the responses to training occurs with consecutive days of exercise. In a study by Suzuki, *et al.,* (1996) acute endurance exercise causes marked peripheral neutrophilia. There were also an associated proportional increase in band neutrophils ($r = 0.727$, $p < 0.05$), suggesting that neutrophils mobilised from the bone marrow following endurance exercise may possess higher responsiveness. On the other hand, the magnitude of the exercise-induced changes was reduced gradually by daily repeated exposure to endurance exercise, but none of the trends were significant except the decline in resting segmented neutrophil counts ($p < 0.05$) at least during a 1-wk period of repeated exercise sessions (Suzuki, *et al.,* 1996).

2.4 MINING OCCUPATIONAL AND ENVIRONMENTAL DESCRIPTION

2.4.1 Environmental Description

In order to investigate possible factors associated with EAMC in mine-workers, it is important to understand the environment they perform their duties in. Since a dearth in literature exist to describe the environmental factors and work conditions of underground miners, the information provided below are anecdotal observations from the researcher.

The physical environment consists of different confined spaces, including gullies, raises and stopes, terminating in the face wall. The stopes are the areas around the face wall where the area of mining needs to advance. There are different stoping heights which include 90cm, 1.2m, 1.5m and higher. Thus the space in which these underground miners perform physical labour can be very confined, forcing them to work in crouched positions for prolonged periods of time (cf. Figure 2.3).

FIGURE 2.3: EXAMPLES OF CROUCHED BODY POSITIONS OF UNDERGROUND MINERS

These crouched body positions of the miners are comparable to the body position of the unfortunate person subjected to the "Scavenger's Daughter" torture device (cf. Figure 2.4) designed during the reign of Henry VIII. This device consisted of a metal A-frame which forced the victim's knees up into a squatting position which induced violent, painful body spasms within a short period of time (Scavenger's daughter, 2011).

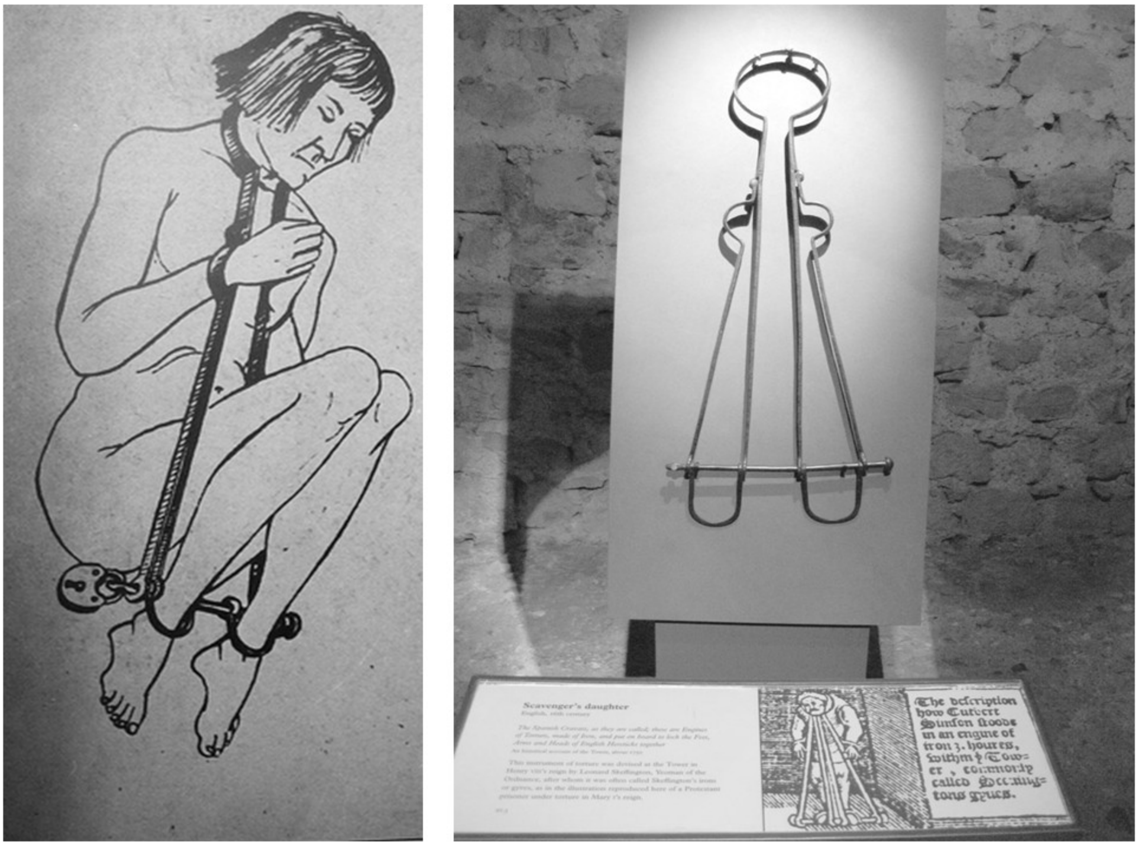

FIGURE 2.4: THE "SCAVENGER'S DAUGHTER" TORTURE DEVICE

Temperature, humidity and air-speed are closely monitored and are subject to mining regulations as specified by the South African Department of Minerals and Resources (DMR). Temperatures must be maintained below 25°C wet bulb and/or 32°C dry bulb and/or 32°C mean radiant temperature (Mine Health and Safety Act, 1996 (Act No. 29 of 1996). These factors are regulated through various strategies including fans (airflow) and ice, and are monitored and recorded on a daily basis. Should the threshold levels be exceeded, work will be suspended in the area until the environmental conditions improve. A high incidence of EAMC is anecdotally expected in the clinic as these variables approach the threshold values. This is echoed in more than 100 years of observational experience in mining and maintains that when the temperature and / humidity increase, more mining employees present with cramps. This in its essence is an historical, observational, evidence-based relationship.

2.4.2 Basic Occupational Descriptions

2.4.2.1 *Machine/Rock-drill operator*

The most common job specification for rock drillers is that of drillers who operate in the stopes. Their job is to drill holes in the rock face using a vibrating drill, mostly supported on a stand, where the dynamite will be placed to blast the rock face for face advancement. The height of the stopes varies, and depending on this height, so do the body positions for drilling. These positions include sitting on their buttocks, squatting and occasionally standing. The rock driller, as part of the development team however, drills for fewer consecutive hours, but their drilling may be into the "roof" of the area. All drillers are exposed to vibrations for extended periods, mostly whilst in a flexed body position. The occupational nature of the machine and rock drill operators can therefore be classified as exercise with physical exertion mostly of a high intensity static nature.

2.4.2.2 *Stope team member*

Stope team members' job specifications vary according to the team they perform their duties in. There are two distinct groups, the stope team members working in the stopes and then the stope team members working in the development team.

Stope team members working in the stopes perform heavy physical labour in the various size stopes. Their jobs mainly consist of building or erecting the packs and support columns that support the roof of the stoping area. Packs are erected by stacking large wooden blocks on each other on the ground until this reaches the roof for support. The occupational nature of the stope team members can therefore be classified as exercise with physical exertion mostly of a high intensity dynamic nature.

Stope team members working in the development teams also perform heavy physical labour. Their function is the clearing and preparation of new area walkways and gulley's where the winch operators, stopers and others need to work.

2.4.2.3 *Winch operator*

The winch operator has more of a sedentary job. They sit behind a winch, a large machine connected to a cable, which in turn connects to a scraper. A scraper is a large scoop that drags the blasted rocks towards the area where it is loaded to be transported away. The winch operator controls the winch by pulling or pushing two large levers to either send the scoop away or bring it back. Occasionally, when the winch rope (a thick metal cable) breaks, they have to repair it by a process called "lashing". Although lashing is a heavy physical job, the occupational nature of a typical winch operator consists mainly of low intensity static exercises. Winch operators also get the most exposure to dust kicked up by the scraper.

2.4.2.4 *Miner's assistant*

The exact job of the miner's assistant depends on whether the assistant works in the development team or in the stoping area. The miner's assistant in the stoping section has a relatively easy job where they carry the dynamite and place them in the drill holes in the face wall. The miner's assistant in the development team performs a more mobile function. They move up and down the raises (tunnels that connect one level to the next) over uneven ground. The occupational nature of the miner's assistants can therefore be classified as exercise with physical exertion mostly of a low intensity dynamic nature.

2.5 HEAT-RELATED ILLNESS

2.5.1 Introduction

Heat disorders have been well described by Leithead and Lind (1964) and in subsequent reviews (Dinman Horvath, 1984; Dukes-Dobos, 1981; Ellis 1976; Knochel, 1974). For the purposes of this study, only a few elements of heat-related illness will be elaborated on.

EAMC is often described as a heat-related illness, and diagnosed as such in the mines. This is evident in the DMR policies regarding miners presenting with cramps. This, even if it is anecdotal, should suggest the role of heat (even as a priming / contributory factor) in the aetiology of cramping. However, in the study by Shearer (1990), 35 of 52 patients that presented with "heat-related illness", presented with cramping as their initial complaint; it was concluded that cramps along with all other symptoms were not associated with age, ambient temperature or serum electrolytes.

2.5.2 Classification of heat-related illness

In a study by Day and Grimshaw (2005), four basic types of heat-related illnesses were described: (1) excessive salt loss with hyponatraemic dehydration, (2) hypokalaemic alkalosis with low serum bicarbonate, (3) haemodilution associated with excessive water intake in stressed individuals, and (4) loss of normal thermoregulation, characterised by high core temperature and paradoxical cessation of sweating. Currently we do not use the above classification when dealing with heat-related illness in the mining sector. We use the available ICD-10 codes as listed in Table 2.1. This classification will probably have to be revisited following the new proposed fatigue- or "altered neuromuscular control" model regarding cramping.

Heat-related illness is classified as an occupational disease and according to the Mine Health and Safety Act (Mine Health and Safety Act, 1996 (Act No. 29 of 1996) is a reportable disease. In the mining sector (against mounting evidence to the contrary), cramping is still considered one of the main and in many cases the first presenting symptom of heat illness.

TABLE 2.1: ICD 10 CODES FOR HEAT RELATED ILLNESS

HEAT (EFFECTS) T67.9	
stroke	T67.0
collapse	T67.1
cramps	T67.2
exhaustion	T67.5
due to	
• salt (and water)	T67.4
• water depletion	T67.3
• with salt depletion	T67.4
• fatigue (transient)	T67.6

Owing to the above available ICD-10 codes on the various different heat-related illnesses, it even further compounds our already murky understanding of the link between heat, cramping and hydration.

The term "heat tetany" (hyperventilation and heat stress) has no official ICD-10 code but is mentioned under heat-related illness. This condition usually results from short periods of stress in intense heat. Symptoms may include hyperventilation, respiratory problems, numbness or tingling, or muscle spasms (Lu, Wang, 2004). Tetany could be considered a protracted period of severe cramping. As seen from the inclusion of heat tetany in the heat-related coding, heat is still considered in the aetiology of cramping.

ICD-10 code T67.2 (Heat cramps) highlights the association between heat and cramps as evidenced by the diagnostic implication of the codes. This is despite emerging evidence that cramping is also associated with other factors, including neuromuscular fatigue (Schwellnuss, *et al.,* 2009). The description on the Johns Hopkins medical website for heat cramps still exists and is still: "Heat cramps are the mildest form of heat injury and consist of painful muscle cramps and spasms that occur during or after intense exercise and sweating in high heat" (Johns Hopkins medicine, n.d.). Thus, here the association between cramping, heat and excessive sweating is still maintained.

In a study by Howe and Boden (2007), which has been cited more than 70 times, heat cramps are described as: "One of the earliest indications of heat illness presents in the form of muscle spasm or muscle cramps." They then go on to say that the above-mentioned typically results after excessive heat exposure leading to profuse sweating. The profuse sweating according to them is compounded by inadequate fluid and electrolyte intake. They also state that sodium loss plays a significant role in exacerbating heat cramps. Evidence for the contribution of magnesium, potassium, or calcium abnormalities to heat cramps is not yet clear. They further motivate heat cramps as a stand-alone entity by saying that it may occur alone or as part of heat exhaustion symptoms (Howe & Boden, 2007). When considering heat cramps as a part of the spectrum of heat exhaustion, it has been suggested the that heat cramps may be beneficial, in that they restrict further effort and possible progress to more severe forms of heat illness, such as heat stroke (Shearer, 1990).

Currently there are many studies dismissing heat as an independent casual risk factor for the development of muscle cramps. Jones (1985) described EAMC in marathon runners in cool temperatures (Jones, *et al.*, 1985) and Laird in triathlete swimmers who have been exposed to extreme cold (Laird, 1989). Then there are also studies showing that EAMC is not directly related to a rise in core temperature (Maughan, 1986) and that passive heating alone and at rest does not result in EAMC (Schwellnus, *et al.*, 1997). Therefore, heat should rather be seen and investigated as one of several possible contributing factors that collectively contribute to the occurrence of cramping. Cramping as an entity, or the mechanism or predisposing factors associated with cramping, should therefore be investigated as a multifactorial challenge that is not confined to singular causative or contributing factors, such as heat.

2.6 CONCLUSION

Miners working underground are exposed to severe working conditions, including extreme heat, humidity and limited nutritional intake. To add to these challenging conditions, this occupation requires strenuous physical labour combined with long, continuous working hours. Interestingly, a dearth of literature exists on EAMC in this population group, despite being exposed to the environmental factors often associated with EAMC. As far as could be established, only a single study (Talbott & Michelsen, 1933) could be found where researchers investigated the prevalence and biochemical findings in persons performing physical labour who presented with what is now termed EAMC (not including all other presenting symptoms of heat illness). The subjects were men employed in the construction of the Hoover Dam in Nevada who, in the course of their work, were exposed to the extreme summer heat of the Colorado River basin desert. Since EAMC is a relatively common occurrence in miners, this population group offers a unique opportunity to investigate both fatigue and electrolyte depletion as possible causes for EAMC. This study contained a large population group, working in a controlled and measurable environment. In previous studies, researchers examined the direct relationship between isolated blood markers and EAMC, but not the blood markers' relationships to each other. Therefore, this study included a more extensive blood profile analysis of miners presenting with EAMC. As far as could be established, this was the first study that will aim to examine a multitude of variables and the prevalence of EAMC in South African underground miners. The value of having a battery of blood tests is that it affords the examiner the opportunity to look at the interactions and relationships between the various blood markers, which as yet have not been done.

This study will aid and expand on our current scientific knowledge, in an area of Sports Medicine that is still plagued by many controversies. EAMC has important implications for training and professional performance, therefore the pursuit of knowledge on its' aetiology is key in the management of this common problem.

It is important to reiterate that this research, as stated above, will aim to lay a foundation for future research, to determine the association of identified factors with EAMC. Special attention will be given to observations made, that will aid in areas of speculative hypotheses for which scientific data is lacking. An example being the relationship between hydration related to hot and humid environmental conditions and EAMC. The missing step, overlooked in previous studies, is the formulation of a control or 'normal' profile of haematological and biochemical changes during a shift, in the mining population. If there is no baseline data associated with a population-specific 'normal' profile, then interpretation of comparative data become misinformed - leading to unsubstantiated and speculative conclusions.

The predictable argument against using the target population in question, to expand our knowledge on EAMC, will be that these patients presented with heat-related illnesses. Although this is a valid point, literature suggest that when seeking a more thorough insight into the physiology of the phenomena that is cramping, we should refrain from unnecessarily compartmentalising or polarising the etiologies, lest we miss the bigger, more complex model of cramping.

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

Chapter 3 will give an overview of the methods used to achieve the aims of this study as set out in Section 1. Considering the definition of Exercise-associated Muscle Cramps (EAMC) (cf. Section 2.1), and the fact that the miners mainly presented with involuntary skeletal muscle contractions during or following a work shift, the use of the term "EAMC" when referring to muscle cramps seemed appropriate and justified within the context of this study.

3.2 AIMS OF THE STUDY

The study aim was twofold:

1. Formulation of a control or 'normal' profile of haematological and biochemical changes during a shift, in the mining population; and
2. Describing the prevalence and certain environmental, biochemical and haematological variables in gold miners working underground who present with exercise-associated muscle cramps (EAMC) at work.

3.3 STUDY DESIGN

This study consisted of two parts:

Part 1 was a retrospective descriptive study of the blood profiles of underground mine workers who presented with EAMC, together with biological factors relating to these workers presenting with EAMC.

Part 2 was a prospective study consisting of a collection of blood-samples, before and after an 8 hour shift (2 hours commuting and 6 hours of physical labour), on a volunteer group of healthy underground mine workers not presenting with cramps. This was done to generate baseline data for a population group not described in literature to date.

Furthermore, this data was generated to assist interpretation of the haematological and biochemical variables from Part 1 of this study.

3.4 STUDY PARTICIPANTS

3.4.1 Study participants for Part 1 (CRA group)

The target population for the cramp group (CRA group) consisted of all underground miners at a South African gold mine who presented at their mine medical stations with a diagnosis of EAMC. A total of 18 430 employed workers worked underground in shifts at the various shafts from June 2010 to December 2011.

3.4.1.1 *Inclusion criteria for the CRA group*

The participants in the CRA group had to:

- be mine workers
- be 18 to 60 years old
- be male or female
- work underground in the specific South African gold mine
- present to the medical services with muscle cramps either during or within 24 hours following a work shift.

3.4.1.2 *Exclusion criteria for the CRA group*

The participants would be excluded from the CRA group if they:

- were not employed at the mine (i.e. illegal miners or zama-zamas);
- were younger than 18 and older than 60 years;
- were not working underground in the specific South African gold mine (i.e. employees working on the surface); and
- presented to the medical services with muscle cramps more than 24 hours following a work shift.

Acute or active illness was initially considered as part of the exclusion criteria for the CRA group. A raised White Cell Count (WCC) would have served as an indication of the presence of said acute illness. This however presented a dual problem owing to the retrospective nature of the data collection for the CRA group (i.e. no history on pre-existing acute illness) as well as the fact that the control group (CON group) showed a WCC reaction pre- to post-shift without concomitant clinical evidence of illness. Consequently, a raised WCC was not considered an exclusion criterion, but rather included for further investigation into the pathophysiology of EAMCs and baseline data for non-cramping underground mine workers.

The number of miners who presented with EAMC and were included in the CRA group amounted to 451 participants.

3.4.2 Study participants for Part 2 (CON group)

The target group of participants in the CON group was comprised of volunteers who presented themselves at the medical station. The participants were all employed at one specific shaft for logistical reasons to assist quality CON of the data collection process. This is in contrast to the cramp group who presented from different shafts in the Free State.

3.4.2.1 *Inclusion criteria for the CON group*

Participants in the CON group had to:

- be mine workers;
- be 18 to 60 years old;
- be male or female;
- work underground in the specific South African gold mine;
- voluntarily present themselves for participation in the study;
- present to the mine medical station before and directly after the same shift;
- not have experienced cramping during the shift;
- have been actively working underground for at least two weeks;
- have no acute illness; and
- be free from EAMC for the 24 hours directly following their work shift.

3.4.2.2 *Exclusion criteria for the CON group*

The participants would be excluded from participating in the CON group if they:

- were not employed at the mine (i.e. illegal miners or zama-zamas);
- were younger than 18 and older than 60 years;
- were not working underground in the specific South African gold mine (i.e. employees working on the surface);
- did not present before and after the same single shift for data and specimen collection;
- presented with cramping during the specific shift or preceding shift;
- presented with EAMC 24 hours after the specific shift; and
- had an acute illness.

Thirty-one volunteers were recruited for the CON group.

3.4.3 Functional grouping of study participants in the CON and CRA groups

The CON- and CRA group study participants were classified into four groups based on the functional nature of their specific job description and its associated type of muscle contraction and level of exertion needed to execute the work. These comprised of (1) static high intensity, (2) dynamic high intensity, (3) static low intensity and (4) dynamic low intensity groups (Table 3.1). Job-specific differences and relationships were considered when analysing the results.

TABLE 3.1: OCCUPATIONAL GROUPING ACCORDING TO EXERTIONAL GRADING

EXERTIONAL GRADING	OCCUPATIONS
Dynamic high intensity	Development team Stope team member
Dynamic low intensity	Miner assistant
Static high intensity	Machine/Rock Driller Stoping
Static low intensity	Scraper Winch Operator Haulage team leader Loader operator Loco operator battery Transport Crew Supervisor Winch erecting Crew Supervisor

3.5 MEASUREMENT

3.5.1 Data collection for the CRA group

The procedure for data collection for the cramp group was to extract routine data from the clinical notes of miners who presented to the medical stations with EAMC.

According to a standard protocol, miners who present with cramps are sent to their mine medical station. At the medical station, the attending nurses complete a standardised medical consultation that is documented on a cramping incident reporting form, as presented in Appendix A. Blood samples are drawn immediately.

After the initial consultation, cramping mine workers are routinely transferred to the mining hospital where they receive normal saline intravenously according to a pre-prescribed regime. After the doctor on call at the emergency unit at the hospital assesses the blood results, the miners are treated and discharged, or admitted to hospital for further treatment if necessary. All results and clinical notes are filed and stored.

As this was a retrospective descriptive study of information already gathered by the mine, the patient records on all the mine-workers presenting with cramps which fit the inclusion criteria were accessed. Data were extracted from these patient files for processing. The study did therefore not interfere with or alter the prescribed management of any miner presenting with cramping.

The personal information (name of patient, name of doctor, name of nurse) appearing on the mine's standard cramping incident reporting forms (Appendix A and B) was not used during the data collection of this retrospective study. The patient number appearing on the mine's standard cramping incident reporting form was used for participant coding in this study to keep track of participants presenting with recurring incidents of EAMC.

3.5.2 Data collection for the CON group

The following procedure was followed for data collection for the prospective part (CON group) of the study:

An invitation to participate in the study was broadcasted on the asbestikum system (video communication system at the mine) at a single mine shaft. Volunteers presented themselves to the mine medical station. When a group of 5 to 10 volunteers were gathered, an information session was convened and the aim of the study, procedures, consent forms, confidentiality and other processes were explained. During this session any queries from the participants were also dealt with. Uncertainty related to the discarding of the blood samples, following the completion of the tests, was raised. This matter was explained accordingly and subsequently added to our consent forms. The consent forms (in English, Xhosa and Sesotho, depending on patient preference) were discussed and explained to the participants after which they signed the forms, granting permission to draw blood samples. A suitable date was chosen on which the tests would be performed both directly before and after the shift, and the participants informed accordingly. These sessions continued until the window of opportunity for data collection had drawn to a close at the end of July 2013.

On the scheduled test day, volunteer participant mine workers presented to the mine medical station prior to their shift, between 04h00-06h00. Basic data and measurements were recorded pre-shift on a standardised form (cf. Appendix C). Baseline blood samples, anthropometric and vital signs measurements were taken before the participants went underground for their normal working shift. Directly after completion of their shift, the participants returned to the medical station where blood samples were drawn again and post-shift data collected (cf. Appendix C). The pre-shift blood samples remained in the fridge to maintain the standard "cold chain" protocol for collecting and transporting blood samples. After the collection of the post-shift blood samples, the researcher, whilst maintaining the cold chain protocol for the collection and transport of blood samples, transported the samples to Pathcare laboratories for processing and analysis.

The blood results were collected from Pathcare laboratories the following day and data extracted into an Excel spreadsheet along with the anthropometric and vital signs information from the pre- and post-shift data collection form (cf. Appendix C). The data were organised in accordance to that of the retrospective cramp group data to assist comparative analyses. There are however discrepancies in the variables reported relating to the symptomatology the workers experienced in the CRA (post-shift) and the CON-group (pre- and post-shift). While there was limited control over the available variables and completeness of patient files for the retrospective data, the aims of this study (cf. Section 3.2) still had to be taken into consideration when planning Part 2 of this study. As a consequence, the additional inclusion of diarrhoea in the CON group was done to consider the possibility of other sources of fluid loss which could affect the workers' hydration statuses. This was done, as part of the aims of the study was to create baseline data for the population group whereas there was limited control over the retrospective data collected for the cramp group.

The data of the prospective study was treated confidentially. The patient number appearing on the reporting form was used as participant coding for this specific study to keep track of the volunteer participants.

3.5.3 Measuring tools

All blood samples were sent to the same Pathcare Laboratory which used a Beckman-Coulter H.max for haematological analyses, a Beckman-Coulter CX9 for biochemistry analyses and a Cobas h232 machine for myoglobin measurements.

The blood tests that are taken as a routine procedure, and were used in this study, included the following presented in Table 3.1 below:

TABLE 3.2: BLOOD TESTS TAKEN FOR THE CON AND CRA GROUP (CALCIUM, MAGNESIUM AND PHOSPHATE WERE NOT TAKEN IN THE CRAMP GROUP)

TEST REQUESTED	TEST INCLUDES	UNITS
Full blood count (FBC)	White cell count (WCC) Lymphocytes Haemoglobin (Hb) Haematocrit (Hct)	(x $10^9.L^{-1}$) (x $10^9.L^{-1}$) ($g.dL^{-1}$) ($g.dL^{-1}$)
Blood glucose	Random blood glucose	($mmol.L^{-1}$)
Myoglobin	Myoglobin	($ng.mL^{-1}$)
CK (total)	Creatine kinase (CK)	($u.L^{-1}$ 37°C)
Liver functions	Total protein Albumin GGT ALK PHOS ALT AST	($g.L^{-1}$) ($g.L^{-1}$) ($u.L^{-1}$ 37°C) ($u.L^{-1}$ 37°C) ($u.L^{-1}$ 37°C) ($u.L^{-1}$ 37°C)
Kidney functions (U&E+Cr)	Urea Creatinine Sodium (Na) Potassium (K) Chloride (Cl) CO_2 MDRD Osmolality$_{(calculated)}$	($mmol.L^{-1}$) ($umol.L^{-1}$) ($mmol.L^{-1}$) ($mmol.L^{-1}$) ($mmol.L^{-1}$) ($mmol.L^{-1}$) ($ml.min^{-1}$) ($mmol.L^{-1}$)
CMP	Calcium Magnesium Phosphate	

The osmolality described in Table 3.2 was calculated by the following formula:

$$\text{Serum osmolality}_{(calculated)}\ (mmol.L^{-1}) = (2 \times Na) + urea + blood\ glucose$$

3.6 METHODOLOGICAL AND MEASUREMENT ERRORS

3.6.1 Measurement errors

3.6.1.1 *CRA group*

The diagnosis of EAMC requires that patients should not have had any acute medical condition at the time of cramping, as medical conditions, specifically infections, in itself, may cause cramping. Initially, in an attempt to correct for the above mentioned, patients that presented with a WCC above 10 (x109.L^{-1}), was to be excluded from the retrospective study or CRA group. However after noticing the increasing WCC in the CON group participants, pre-shift to post shift, it was decided to keep the participants with a WCC > 10 as part of the CRA group as there appears to be a WCC response (raised WCC) regardless of whether the participants had an acute infection. Thus the raised WCC need not necessarily have indicated an acute infective state in the CRA group as there was no "pre-shift" WCC on these patients, where a raised WCC would suggest an active infective process.

Core temperature could have been operator dependent, as different nurses were taking the temperatures at the different mine medical stations. The nursing staff, as part of their training, receives training on the reading and corrects techniques of taking oral and rectal temperatures. The instrumentation at all medical stations were similar during the time of data collection.

3.6.1.2 *CON group*

An attempt was made to minimise measurement errors by assigning the researcher the sole responsibility of collecting and measuring the CON group data. The same laboratory (Pathcare) performed the same tests, as was the case with the retrospective part of the study. They also used the same techniques and machines to perform the tests as with the CRA group data.

3.6.2 Variations in our participant sample size

The sample size of the CRA group included all miners working underground in one of the South African gold mines that presented to the medical services with muscle cramps during or within 24h following a work shift between Jun 2010 and Dec 2011.

In the CON group the initial goal of achieving a minimum of 50 participants was not achieved due to time constraints and a lack of volunteers. A total of 31 participants for CON group had to be accepted.

3.6.3 Methodological errors

3.6.3.1 *CON group*

The pre-shift blood samples that were stored in the fridge from the time of collection up to post-shift collection time (an average of 9 hours) had shown haemolysis prior to the sample processing by the laboratory. This occurred as there is only a single daily collection of samples at the shafts. This resulted in abnormally high potassium levels which were taken into consideration for the interpretation and discussion of findings in Chapter 5.

3.7 PILOT STUDY

3.7.1 The CRA group

Since the mine's "Work place information for suspected heat illness cases" (Appendix A) is a standard format, the information (excluding personal information) was transferred in the same format into Excel. A pilot study was done using 10 patient records to become acquainted with the transfer of the data into Excel. The pilot study did not indicate any potential problems with the layout of the Excel sheet for analyses and consequently no changes were made to the layout of the data extraction sheet in Excel.

3.7.2 The CON group

A pilot study was undertaken to validate the consent form and its contents. The addition of a section to explain the discarding of their blood samples following processing by the laboratory was added to the consent form.

The completion and coding of the data collection forms (Appendix C) were assessed. No apparent problems with the forms or the procedures for collecting the information and measurements from the participants were identified. The anthropometric measurements were not part of the retrospective collected data, but was included in the prospective study to facilitate the formulation of normative or baseline data for this population. This is the reason for the inclusion of these measurements in the pilot study.

3.8 ANALYSIS OF THE DATA

The data were entered into an Excel spreadsheet and sent to the Department of Biostatistics, University of the Free State, for statistical analyses. Due to the exploratory nature of this study, descriptive statistics were primarily used to report the findings. The data were generally not normally distributed and consequently results were summarised using medians and percentiles where appropriate. For comparison of categorical variables, the Chi^2 and Fisher-exact tests were used as appropriate, while 95% confidence intervals were used to assess differences between the medians of paired scale data sets.

3.9 IMPLEMENTATION OF FINDINGS

This study will be used to identify trends in the generated data, through the interpretation of comprehensive blood profiles of gold miners working underground that presented with EAMC. As far as could be established, this is the first study to explore the pathophysiology of EAMC in miners utilising such comprehensive blood profiles. These data have not been analysed and published before, and will present novel findings to improve our understanding of EAMC.

3.10 ETHICS

The study commenced after ethical approval had been granted by the Ethics Committee (ECUFS number 198/2011), Faculty of Health Sciences at the University of the Free State. No conflict of interest was applicable in this study. All data were handled with confidentiality and reported anonymously.

In Part One of the study (CRA group), in workers presenting with EAMC at work, existing data were extracted from patient files and consequently no informed consent was obtained. The mine consented to the research taking place and had given their approval that patient files be accessed to collect data pertaining to EAMC (Appendix B).

In Part Two (CON group), during the pilot study, following the pre-test counselling sessions, the participants were asked to repeat their understanding of the process in their own words. Their responses were scrutinised and any corrections fed back to the participants by a professional nurse that spoke the same language as the participant. Hereafter an opportunity was offered to the prospective participant to raise any questions or concerns, which were then addressed. Prior to enrolling a participant in the prospective study, informed consent was obtained. The participation in the prospective part was completely voluntary.

All participants received unbiased and appropriate medical treatment at all times during the study. Doctor-patient confidentiality was upheld at all stages during the study and no information on the individual medical information was made available to the employer that may have influenced the mine-employees occupation adversely.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

In this chapter, the results obtained of possible factors associated with exercise-associated muscle cramps (EAMC), as well as findings on the "normal" physiological changes during a shift of a person doing physical labour in an underground mining environment are presented. Considering that the cramp group (CRA) data were collected after a work shift, the CRA group data are presented as $CRA_{(post)}$. Similarly, the control group (CON) data are presented as $CON_{(pre)}$ and $CON_{(post)}$ for the data collected before and after the work shift respectively.

Shapiro-Wilk tests confirmed non-parametric distributions for several parameters. Variables which displayed parametric distributions across all three group categories ($CON_{(pre)}$, $CON_{(post)}$ and $CRA_{(post)}$) were summarised using means ($\bar{x}$) and standard deviations (sd). Where one or more of the group categories displayed a non-parametric distribution, data were summarised using the lower (Q_1, 25th percentile) and upper (Q_3, 75th percentile) quartile distributions around the median (M). Differences were calculated using 95% confidence intervals (CI) and significance set at $p \leq 0.05$ for all other comparative statistical tests.

Chapter 4 is divided into two parts. The first part concerns the comparative data between the CON and CRA groups. The second part presents the findings for the CON group aimed at establishing baseline data for underground miners and the haematological and biomechanical changes following a typical underground work shift.

4.2 CRAMP VS. CONTROL COMPARATIVE DATA

4.2.1 Demographics

The CRA group consisted of 386-450 miners (depending on the completeness of the mine's patient files) who presented to the mine medical station with exercise-associated muscle cramps (EAMC) during or within 24 hours following a work shift. The CON group consisted of 31 volunteers who did not present with EAMC during or within 24 hours following a work shift.

4.2.1.1 *Occurrence of cramping*

Underground miners presented to the mine medical station with EAMCs throughout the week. Below is the distribution of CRA group participants according to each respective day of the week on which they presented with EAMCs.

TABLE 4.1: OCCURRENCE OF CRAMPING (DAY OF THE WEEK)

DAY OF THE WEEK	NUMBER OF PRESENTATIONS (n)	PERCENTAGE OF TOTAL CRA GROUP
Monday	61	13.6%
Tuesday	126	28.0%
Wednesday	112	24.9%
Thursday	73	16.2%
Friday	50	11.1%
Saturday	24	5.3%
Sunday	4	0.9%

From the Table 4.1 it can be seen that miners seemingly presented with EAMCs more often on a Tuesday and Wednesday, evidenced by the fact that just over half (52.9%) of the CRA group participants presented on these two days (combined). Mondays (13.6%), Thursdays (16.2%) and Fridays (11.1%) showed similar distributions in the number of cramping miners presenting to the medical station, while only a few (proportionate to the total number of CRA group participants) presented with EAMCs over the weekend (Saturdays and Sundays, 5.3% and 0.9% respectively). It is important to mention that the CON group data were collected on a Wednesday and therefore appropriate for comparison to the CRA group.

4.2.1.2 *Physical nature of specific occupations for the CON and CRA groups*

Below is the proportionate representation of participants within each job description group.

TABLE 4.2: PHYSICAL NATURE OF SPECIFIC OCCUPATIONS FOR THE CON AND CRA GROUPS

	CON (n = 31)	CRA (n = 444)
Dynamic, high intensity (%)	22.58	18.47
Dynamic, low intensity (%)	12.90	17.57
Static, high intensity (%)	25.81	38.74
Static, low intensity (%)	38.71	25.23

p = 0.270

The highest number of CRA miners performed work tasks of high intensity and a static nature (38.74%), being approximately double of those who performed dynamic tasks of either a high (18.47%) or low intensity (17.57%). When combining the incidence of cramps within the CRA miners performing work tasks of a static nature, regardless of the intensity, it amounted to 63.97% of the total number of cramps reported at the medical centre. The static work task groups were evenly represented by the CRA (63.97%) and CON (64.52%) groups. When comparing the dispersion of CON and CRA participants within each job description category to each other, no significant difference (p = 0.270) was found.

4.2.2 Illness profile

TABLE 4.2.1: POSITIVE MEDICAL HISTORIES FOR THE CON AND CRA GROUPS

	CON (n = 31)	CRA (n = 450)	p
Chronic illness (%)	45.16	12.22	< 0.001*
Previous cramps (%)	22.58	23.48	0.909

**Statistical significance*

A substantial 45.15% of the CON group reported a history of chronic illness, which was significantly more (p < 0.001) compared to the mere 12.22% of the CRA group who had a history of chronic illnesses when presenting with EAMCs. There was no difference (p 0.909) between the CON (22.58%) and CRA (23.48%) group regarding a previous history of cramping.

4.2.3 Symptoms and vital signs

4.2.3.1 *Physical symptoms experienced following a shift*

The screening of symptoms experienced following a shift were scrutinised under two categories; those specified in direct questioning and those left to open response when asking the participants to report "any other symptoms". During data collection of the

CON group, some of the specified symptoms from the CRA were moved to the open response section during the post-shift interview. This decision was made to save time during the questioning as a lot had to be done in a short period of time prior to the participants descending for their shift. The author however acknowledges this decisions resultant limitation on the data interpretation.

TABLE 4.3: PHYSICAL SYMPTOMS EXPERIENCED FOLLOWING A SHIFT

TYPE OF QUESTIONING	SYMPTOM	CON (n = 31)	CRA (n = 444)	p
a	Dizziness	3.23	47.65	< 0.001*
	Nausea	9.68	40.27	< 0.001*
	Vomiting	0.00	18.12	0.009*
b	Fainting	0.00	4.03	NP
	Confusion	0.00	10.29	NP
	Headache	0.00	41.61	NP
	Aggression	0.00	1.79	NP
	Abdominal pain	0.00	38.93	NP
c	Diarrhoea	0.00	0.00	NP

*Statistical significance; NP = Not possible (to determine statistically); a = direct questioning in both groups; b = direct questioning in CRA group and open response in CON group; c = direct questioning in CON group and open response in CRA group.

From Table 4.3 it can be seen that the CRA group presented with significantly more accompanying symptoms of dizziness (47.65%, $p < 0.001$), nausea (40.27%, $p < 0.001$) and vomiting (18.12%, $p = 0.009$) compared to that reported by the CON group, even under direct questioning (a). From the category of open response symptoms in the CON group (b), none of the CON participants reported abdominal pain or headaches, compared to the substantial proportion of CRA participants who complained of headaches (41.61%) and abdominal pain (38.93%) when reporting to the medical centre with EAMC. Symptoms such as fainting (4.03%), confusion (10.29%) and aggression (1.79%) were less prevalent than headaches and abdominal pain in the CRA group and seemingly absent in the CON group.

4.2.3.2 *Vital signs*

Only body temperature is presented below since blood pressure and heart rate data were only available for the CON group and therefore presented in the second part of Chapter 4 (cf. Section 4.1).

TABLE 4.4: BODY TEMPERATURE FOR THE CON AND CRA GROUP

BODY TEMPERATURE (°C)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	35.1	36.0	36.3	0.144 [-0.2 ; 0.7]	
$CON_{(post)}$	35.7	36.2	36.5		0.001* [0.2 ; 0.6]*
$CRA_{(post)}$	36.1	36.5	36.9		

**Statistical significance*

The CON group displayed similar ($p = 0.144$, CI = -0.2 ; 0.7) body temperatures before (M = 36.0°C) and after (M = 36.2°C) their work shift. When comparing the $CON_{(post)}$ and $CRA_{(post)}$ group data, significantly higher ($p = 0.001$, CI = 0.2 ; 0.6) body temperatures were seen for the CRA group.

4.2.4 *Fluid intake*

Below are the self-reported fluid intakes of the CON and CRA groups during the specific work shift associated with the data collection.

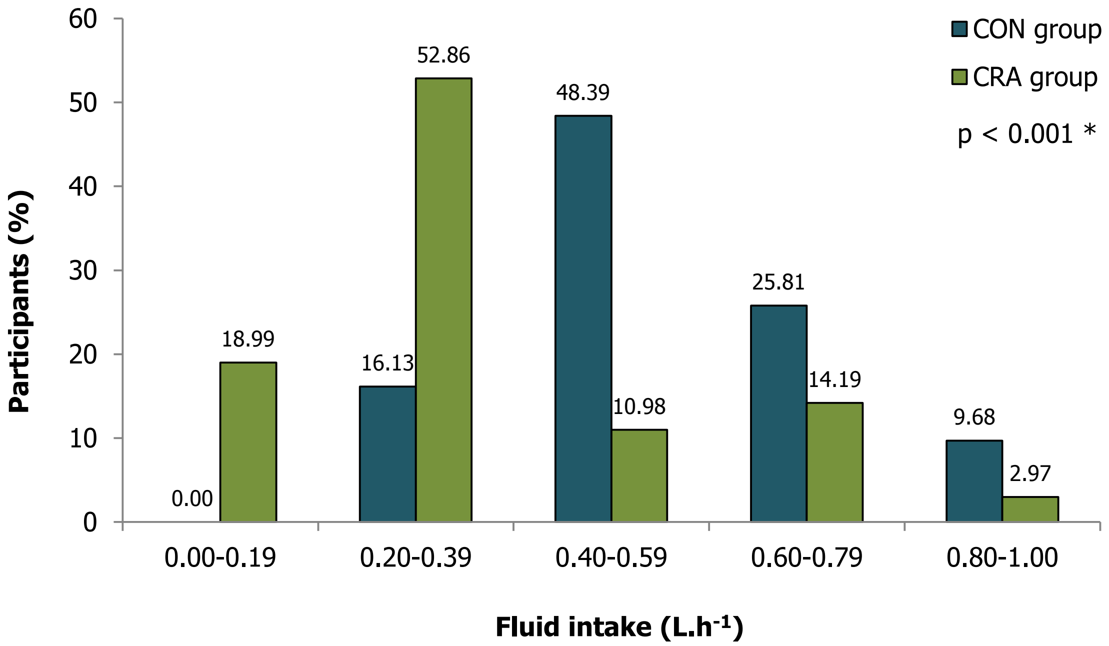

FIGURE 4.1: THE SELF-REPORTED FLUID INTAKES OF THE CON AND CRA GROUPS DURING THEIR WORK SHIFTS

Figure 4.1 shows a marked difference between the fluid intakes of the CON and the CRA groups. The CON group drank significantly ($p < 0.001$) more fluid during their shift compared to the CRA group. The majority (52.86%) CRA group participants had a fluid intake of 0.20 – 0.39 $L.h^{-1}$ while just under half (48.39%) of the CON group had a fluid intake of 0.40–0.59 $L.h^{-1}$ during a shift. None of the CON group drank less than 0.19 $L.h^{-1}$, compared to a substantial portion (18.99%) of the CRA group which did. When looking at the highest fluid intake category (0.80 to 1.00 $L.h^{-1}$), a mere 2.97% of the CRA group fell within this category compared to the 9.68% of the CON group.

4.2.5 Blood profiles

The blood results were grouped in four main categories; (1) full blood count, (2) liver functions, (3) electrolytes, renal function and hydration and (4) muscle damage markers.

4.2.5.1 *Full blood count*

The full blood count included the white cell count (WCC), lymphocytes, haemoglobin (Hb) and haematocrit (Hct).

TABLE 4.5.1: WHITE CELL COUNTS (WCC) OF THE CON AND CRA GROUPS

WCC ($x10^9.L^{-1}$)	Q_1	M	Q_3	p [CI]	
CON$_{(pre)}$	5.2	6.2	6.6	0.026* [-0.2 ; 0.9]	
CON$_{(post)}$	5.4	6.5	7.3		< 0.001* [0.9 ; 2.8]*
CRA$_{(post)}$	6.3	8.3	10.8		

**Statistical significance*

The CON$_{(post)}$ group displayed a median WCC of 6.5 x $10^9.L^{-1}$ following their work shift which was slightly yet significantly higher ($p = 0.026$) than the CON$_{(pre)}$ WCC of 6.2 x $10^9.L^{-1}$ before their work shift. The CRA group presented with a median WCC of 8.3 x $10^9.L^{-1}$ when presenting to the medical centre with EAMC during or after a shift, which was significantly higher ($p < 0.001$) compared to the WCC of the CON$_{(post)}$ group following a work shift.

TABLE 4.5.2: LYMPHOCYTES OF THE CON AND CRA GROUPS

LYMPHOCYTES ($x10^9.L^{-1}$)	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	2.3 ± 0.5	0.044* [-0.4 ; 0.5]	
$CON_{(post)}$	2.5 ± 0.7		< 0.001* [-0.9 ; -0.4]*
$CRA_{(post)}$	1.9 ± 0.8		

**Statistical significance*

The CON group presented with an average lymphocyte concentration of 2.3 ± 0.5 $x10^9.L^{-1}$ before their work shift, which increased significantly (p = 0.044) to an average lymphocyte concentration of 2.5 ± 0.7 $x10^9.L^{-1}$ after their work shift. This was significantly higher (p < 0.001, CI = -0.9; -0.4) than the average CRA group lymphocyte concentration of 1.9 ± 0.8 $x10^9.L^{-1}$ (Table 4.5.2).

TABLE 4.5.3: HAEMOGLOBIN OF THE CON AND CRA GROUPS

HAEMOGLOBIN ($g.L^{-1}$)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	13.6	14.6	15.0	0.003* [-0.9 ; -0.2]*	
$CON_{(post)}$	12.9	14.1	14.7		< 0.001* [1.1 ; 2.3]*
$CRA_{(post)}$	14.3	15.6	16.8		

**Statistical significance*

Before the start of the shift, the median $CON_{(pre)}$ Hb measured at 14.6 $g.L^{-1}$ which decreased significantly (p = 0.003, CI = -0.9 ; -0.2) during the course of the work shift to a median $CON_{(post)}$ Hb measurement of 14.1 $g.L^{-1}$ after the work shift. The CRA group had a median Hb measurement of 15.6 $g.L^{-1}$ which was significantly higher (p < 0.001, CI = 1.1 ; 2.3) compared to the $CON_{(post)}$ Hb measurement.

TABLE 4.5.4: HAEMATOCRIT OF THE CON AND CRA GROUPS

Hct ($x10^9.L^{-1}$)	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	0.43 ± 0.03	0.001* [-0.03 ; -0.01]*	
$CON_{(post)}$	0.41 ± 0.04		< 0.001* [0.03 ; 0.06]*
$CRA_{(post)}$	0.46 ± 0.05		

*Statistical significance

The CON group Hct showed a significant (p = 0.001, CI = -0.03 ; -0.01) decrease in concentration from $CON_{(pre)}$ 0.43 ± 0.03 $x10^9.L^{-1}$ to $CON_{(post)}$ 0.41 ± 0.04 $x10^9.L^{-1}$. When comparing the $CRA_{(post)}$ Hct to the $CON_{(post)}$ Hct concentrations, the $CRA_{(post)}$ group presented with a significantly higher (p < 0.001, CI = 0.03 ; 0.06) Hct of 0.46 ± 0.05 x $10^9.L^{-1}$.

4.2.5.2 *Liver functions*

The liver functions test included total protein measurements, albumin (Alb), Alkaline phosphatase (ALP), Gamma-glutamyl transpeptidase (GGT), Alanine transaminase (ALT) and Aspartate aminotransferase (AST).

TABLE 4.6.1: TOTAL PROTEIN OF THE CON AND CRA GROUPS

<table>
<tr><th>Total protein ($g.L^{-1}$)</th><th>Q_1</th><th>M</th><th>Q_3</th><th colspan="2">p
[CI]</th></tr>
<tr><td>$CON_{(pre)}$</td><td>70.0</td><td>78.0</td><td>83.0</td><td rowspan="2">0.004*
[0.0 ; 5.0]</td><td></td></tr>
<tr><td>$CON_{(post)}$</td><td>75.0</td><td>81.0</td><td>86.0</td><td rowspan="2">< 0.001*
[6.0 ; 15.0]*</td></tr>
<tr><td>$CRA_{(post)}$</td><td>81.0</td><td>90.0</td><td>102.0</td><td></td></tr>
</table>

**Statistical significance*

From Table 4.6.1 it can be seen that the Total protein values shows an insignificant (p = 0.004) increase from $CON_{(pre)}$ 78.0 $g.L^{-1}$ to $CON_{(post)}$ 81.0 $g.L^{-1}$ in the CON group. When comparing the $CON_{(post)}$ group to the CRA however, the CRA shows a significantly higher total serum protein $CON_{(post)}$ 81 $g.L^{-1}$ vs. CRA 90 $g.L^{-1}$ (p < 0.001 , CI = 6 ; 15).

TABLE 4.6.2: ALBUMIN OF THE CON AND CRA GROUPS

<table>
<tr><th>ALBUMIN ($g.L^{-1}$)</th><th>$\bar{x}$ ± sd</th><th colspan="2">p
[CI]</th></tr>
<tr><td>$CON_{(pre)}$</td><td>38.5 ± 3.9</td><td rowspan="2">< 0.001*
[1.0 ; 4.0]*</td><td></td></tr>
<tr><td>$CON_{(post)}$</td><td>41.6 ± 4.3</td><td rowspan="2">0.005*
[2.0 ; 7.0]*</td></tr>
<tr><td>$CRA_{(post)}$</td><td>46.2 ± 9.1</td><td></td></tr>
</table>

**Statistical significance*

When relating the total protein in Table 4.6.1 to the serum albumin in Table 4.6.2, there was a concomitant significant (p < 0.001 , CI = 1.0 ; 4.0) increase in mean serum albumin levels $CON_{(pre)}$ 38.5 ± 3.9 $g.L^{-1}$ to $CON_{(post)}$ 41.6 ± 4.3 $g.L^{-1}$ in the $CON_{(group).}$ With the 3.6 $g.L^{-1}$ increase in the total protein $CON_{(pre)}$ to $CON_{(post)}$ one can see from the concomitant 3.1 $g.L^{-1}$ increase in the albumin contribution that the increase in total protein was as a result of an increase in albumin. When comparing the $CON_{(post)}$ group to the CRA group, the CRA group shows a significantly higher mean Albumin serum content $CON_{(post)}$ 41.6 ± 4.3 $g.L^{-1}$ vs. CRA 46.2 ± 9.1 $g.L^{-1}$ (p = 0.005 , CI = 2.0 ; 7.0). The percentage contribution of albumin to the higher total protein was at roughly 50% in this group.

TABLE 4.6.3: ALKALINE PHOSPHATASE OF THE CON AND CRA GROUPS

Alkaline phosphatase ($u.L^{-1}$ 37°C) (ALP)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	59.0	72.0	86.0	0.012* [-8.0 ; 0.0]	
$CON_{(post)}$	55.0	64.0	82.0		0.001* [6.0 ; 22.0]*
$CRA_{(post)}$	66.0	81.0	98.0		

Statistical significance

From Table 4.6.3 it can be seen that the serum ALP significantly ($p = 0.012$) decreased from 72.0 $u.L^{-1}$ 37°C $CON_{(pre)}$ to 64.0 $u.L^{-1}$ 37°C $CON_{(post)}$. The CRA group (81.0 $u.L^{-1}$ 37°C) on the other and showed a significantly higher ($p = 0.001$, CI = 6.0 ; 22.0) serum ALP than the median $CON_{(post)}$ values.

TABLE 4.6.4: GAMMA-GLUTAMYL TRANSPEPTIDASE OF THE CON AND CRA GROUPS

Gamma-glutamyl transpeptidase ($u.L^{-1}$ 37°C) (GGT)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	14.0	27.0	38.0	0.248 [-1.0 ; 3.0]	
$CON_{(post)}$	16.0	28.0	40.0		0.029* [1.0 ; 13.0]*
$CRA_{(post)}$	23.0	31.0	48.0		

Statistical significance

Serum GGT (Table 4.6.4) did not show a significant difference $CON_{(pre)}$ to $CON_{(post)}$. The CRA did show a slight but significantly higher ($p = 0.029$, CI = 1.0 ; 13.0) serum GGT median 31.0 $u.L^{-1}$ 37°C compared to the CON(post) group at 28.0 $u.L^{-1}$ 37°C.

TABLE 4.6.5: ALANINE TRANSAMINASE OF THE CON AND CRA GROUPS

Alanine transaminase ($u.L^{-1}$ 37°C) (ALT)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	20.0	24.0	34.0	0.372 [-1.0 ; 3.0]	
$CON_{(post)}$	21.0	25.0	35.0		0.531 [-2.0 ; 5.0]
$CRA_{(post)}$	21.0	27.0	36.0		

The serum ALT again did not show a significant change $CON_{(pre)}$ to $CON_{(post)}$. The CRA similarly did not show a significant difference compared to the $CON_{(post)}$ group.

TABLE 4.6.6: ASPARTATE AMINOTRANSFERASE OF THE CON AND CRA GROUPS

Aspartate aminotransferase ($u.L^{-1}$ 37°C) (AST)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	25.0	33.0	41.0	0.255 [-1.0 ; 3.0]	
$CON_{(post)}$	27.0	34.0	43.0		0.203 [-1.0 ; 8.0]
$CRA_{(post)}$	29.0	36.0	50.0		

As seen from Table 4.6.6, there was not a significant difference between the $CON_{(pre)}$ and $CON_{(post)}$ or the $CON_{(post)}$ and CRA group results.

4.2.5.3 Electrolytes, renal function and hydration

This section on Electrolytes, renal function and hydration contains results for: urea, creatinine (Cr), sodium (Na), chloride (Cl), potassium (K), Modification of Diet in Renal Disease ($ml.min^{-1}$) (MDRD) or Glomerular Filtration Rate (GFR), CO_2, and calculated osmolality.

TABLE 4.7.1: UREA COUNT OF THE CON AND CRA GROUP

Urea ($mmol.L^{-1}$)	$\bar{x} \pm sd$	p [CI]	
$CON_{(pre)}$	5.0 ± 2.1	0.438 [-0.7 ; 0.3]	
$CON_{(post)}$	4.9 ± 2.4		< 0.001* [2.0 ; 3.8]*
$CRA_{(post)}$	7.8 ± 3.1		

**Statistical significance*

In Table 4.7.1 $CON_{(pre)}$, 5.0 ± 2.1 $mmol.L^{-1}$, to $CON_{(post)}$, 4.9 ± 2.4 $mmol.L^{-1}$ serum Urea levels in the CON group showed an insignificant decrease ($p = 0.438$). The CRA mean value of 7.8 ± 3.1 $mmol.L^{-1}$ in comparison showed a significantly higher urea ($p < 0.001$, CI = 2.0 ; 3.8) compared to the $CON_{(post)}$ values.

TABLE 4.7.2: CREATININE COUNT OF THE CON AND CRA GROUP

Creatinine ($\mu mol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	80 ± 21	0.049* [0 ; 9]	
$CON_{(post)}$	88 ± 38		< 0.001* [35 ; 99]*
$CRA_{(post)}$	166 ± 123		

**Statistical significance*

Similarly in Table 4.7.2 the $CON_{(pre)}$ creatinine mean of 80 ± 21 $\mu mol.L^{-1}$ showed a slight statistically significant ($p = 0.049$) increase to $CON_{(post)}$ 88 ± 38 $\mu mol.L^{-1}$ values whereas the CRA values 166 ± 123 $\mu mol.L^{-1}$ showed a significantly ($p < 0.001$, CI = 35 ; 99) higher mean value than the $CON_{(post)}$ values.

TABLE 4.7.3: SODIUM COUNT OF THE CON AND CRA GROUP

Sodium ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	137 ± 3	0.012* [-3 ; 0]	
$CON_{(post)}$	135 ± 3		0.232 [0 ; 2]
$CRA_{(post)}$	136 ± 4		

**Statistical significance*

The serum sodium levels in Table 4.7.3 showed a slight but significant ($p = 0.012$) decrease $CON_{(pre)}$ 137 ± 3 $mmol.L^{-1}$ to $CON_{(post)}$ 135 ± 3 $mmol.L^{-1}$. The mean values for the $CON_{(post)}$ group and the CRA group did not show a significant difference ($p = 0.232$) when considered in isolation.

TABLE 4.7.4: CHLORIDE COUNT OF THE CON AND CRA GROUP

Chloride ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	104 ± 3	< 0.001* [-4 ; -1]*	
$CON_{(post)}$	101 ± 3		0.026* [-4 ; 0]
$CRA_{(post)}$	99 ± 5		

**Statistical significance*

As seen in Table 4.7.4, serum chloride showed a small statistically significant ($p < 0.001$, CI = -4 ; -1) decrease $CON_{(pre)}$ 104 ± 3 $mmol.L^{-1}$ to $CON_{(post)}$ 101 ± 3 $mmol.L^{-1}$ in the CON group. There was a significantly ($p=0.026$) lower mean when comparing the CRA values 99 ± 5 $mmol.L^{-1}$ to the $CON_{(post)}$ group values.

TABLE 4.7.5: POTASSIUM COUNT OF THE CON AND CRA GROUP

Potassium (mmol.L^{-1})	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	5.4 ± 0.8	0.001* [-1.2 ; -0.2]*	
$CON_{(post)}$	4.7 ± 0.9		0.062 [-0.4 ; 0.1]
$CRA_{(post)}$	4.7 ± 0.7		

**Statistical significance*

In Table 4.7.5 in the CON group, mean potassium levels $CON_{(pre)}$ 5.4 ± 0.8 mmol.L^{-1} to $CON_{(post)}$ 4.7 ± 0.9 mmol.L^{-1} showed a significant (p = 0.001 , -1.2 ; -0.2) decrease. The CRA potassium mean was 4.5 ± 0.7 mmol.L^{-1} which, when compared to the $CON_{(post)}$ values in the CON group did not show a significant difference (p = 0.062).

TABLE 4.7.6: GLOMERULAR FILTRATION RATE OF THE CON AND CRA GROUP

Glomerular filtration rate (ml.min^{-1})	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	77.5	90.0	90.0	0.003* [-5.0 ; 0.0]	
$CON_{(post)}$	71.0	85.0	90.0		<0.001* [-43 ; -18]*
$CRA_{(post)}$	28.0	41.0	79.0		

**Statistical significance*

The median Modification of Diet in Renal Disease (MDRD) or Glomerular filtration rate (GFR) showed a slight but significant (p = 0.003) decrease $CON_{(pre)}$ 90 ml.min^{-1} to $CON_{(post)}$ 85.0 ml.min^{-1} in Table 4.7.6. The CRA median MDRD/GFR showed a significantly (p < 0.001 , CI = -43 ; -18) lower value of 41.0 ml.min^{-1} when compared to the $CON_{(post)}$ mean in the CON group.

TABLE 4.7.7: CO_2 OF THE CON AND CRA GROUP

CO_2 (mmol.L^{-1})	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	25.6 ± 2.5	0.881 [-2.0 ; 1.4]	
$CON_{(post)}$	25.7 ± 2.3		< 0.001* [-3.0 ; -0.9]*
$CRA_{(post)}$	23.7 ± 3.1		

**Statistical significance*

The CO2 in Table 4.7.7 did not show a significant (p = 0.881) increase from $CON_{(pre)}$ to $CON_{(post)}$ in the CON group. However, when you compare the mean CRA values 23.7 ± 3.1 mmol.L^{-1} to the mean $CON_{(post)}$ value 25.7 ± 2.3 mmol.L^{-1}, the CRA values shows a slight but significantly lower mean value (p < 0.001 , CI = -3.0 ; -0.9).

TABLE 4.7.8: OSMOLALITY OF THE CON AND CRA GROUP

Osmolality (mmol.L^{-1})	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	284 ± 5.9	0.003* [-8.4 ; -0.9]*	
$CON_{(post)}$	280 ± 5.3		0.522 [3.4 ; 8.0]*
$CRA_{(post)}$	283 ± 27.2		

**Statistical significance*

The calculated osmolality in Table 4.7.8 shows a statistically significant ($p = 0.003$ CI -8.4 ; -0.9) decrease $CON_{(pre)}$ 284 ± 5.9 mmol.L^{-1} to $CON_{(post)}$ 280 ± 5.3 mmol.L^{-1} in the CON group. When comparing the CRA results 283 ± 27.23 mmol.L^{-1} to the $CON_{(post)}$ result, there is a significantly higher value (CI = 3.4 ; 8.0) in the CRA. This CRA value is however very similar to the $CON_{(pre)}$ value when looking at the means.

TABLE 4.7.9: BLOOD GLUCOSE OF THE CON AND CRA GROUP

Blood glucose (mmol.L^{-1})	$\bar{x}$ ± sd	p [CI]	
$CON_{(pre)}$	5.3 ± 1.4	0.012* [-0.2 ; -1.3]*	
$CON_{(post)}$	4.6 ± 0.7		< 0.001* [1.1 ; 1.7]*
$CRA_{(post)}$	5.9 ± 1.8		

**Statistical significance*

As seen in Table 4.7.9 above, the serum glucose mean value showed a small but significant ($p = 0.012$, CI -0.2 ; -1.3) decrease in the $CON_{(pre)}$ 5.3 ± 1.4 mmol.L^{-1} to $CON_{(post)}$ group 4.6 ± 0.7 mmol.L^{-1} values. The CRA group on the other hand showed a small but significantly ($p < 0.001$, CI = 1.1 ; 1.7) higher mean serum glucose value of 5.9 ± 1.8 mmol.L^{-1} compared to the $CON_{(post)}$ group.

4.2.5.4 Muscle damage markers

This section on muscle damage markers includes creatine kinase (CK) and myoglobin results.

TABLE 4.8.1: CREATINE KINASE OF THE CON AND CRA GROUP

CK (units.L^{-1} 37°C)	Q_1	M	Q_3	p [CI]	
$CON_{(pre)}$	166	247	335	< 0.001* [21 ; 66]*	
$CON_{(post)}$	206	307	433		0.222 [-24; 117]
$CRA_{(post)}$	221	331	581		

**Statistical significance*

Table 4.8.1 showed that the median CON$_{(pre)}$ creatine kinase level 247 units.L^{-1} 37°C is followed by a significant ($p < 0.001$, CI = 21 ; 66) increase in the creatine kinase level in the CON$_{(post)}$ results 307 units.L^{-1} 37°C. Creatine kinase levels in the CRA 331 units. L^{-1} 37°C, when compared to the CON$_{(post),}$ did not show a significant change ($p = 0.222$).

TABLE 4.8.2: MYOGLOBIN OF THE CON AND CRA GROUP

<table>
<tr><th>Myoglobin (ng.mL^{-1})</th><th>Q_1</th><th>M</th><th>Q_3</th><th colspan="2">p
[CI]</th></tr>
<tr><td>CON$_{(pre)}$</td><td>19.8</td><td>27.5</td><td>41.0</td><td rowspan="2">0.713
[4.0 ; 26.0]*</td><td></td></tr>
<tr><td>CON$_{(post)}$</td><td>25.0</td><td>51.0</td><td>68.0</td><td rowspan="2">< 0.001*
[60.0 ; 230.0]*</td></tr>
<tr><td>CRA$_{(post)}$</td><td>61.3</td><td>186.5</td><td>545.0</td><td></td></tr>
</table>

**Statistical significance*

The mean CON$_{(pre)}$ myoglobin 27.5 ng.mL^{-1} in Table 4.8.2 showed a small but significant (CI = 4.0 ; 26) increase in the CON$_{(post)}$ results 51.0 ng.mL^{-1}. Myoglobin did show a significantly higher ($p < 0.001$, CI = 66.0 ; 230) value when comparing the mean CRA 186.5 ng.mL^{-1} to the CON$_{(post)}$ group.

4.3 CON GROUP EXTRA INFORMATION FOR COMPILING NORMATIVE DATA

4.3.1 Anthropometric profile of the CON-group, pre-shift and post-shift

Table 4.9 relates solely to the CON group of the study as the cramp group did not have the pre-shift measurements with which to compare the post-shift findings.

TABLE 4.9.1: BODY MASS OF THE CON GROUP

<table>
<tr><th>Body mass (kg)</th><th>$\bar{x}$ ± sd</th><th>p
[CI]</th></tr>
<tr><td>CON$_{(pre)}$</td><td>71.8 ± 10.1</td><td rowspan="2">< 0.001*
[-2.1 ; -0.6]*</td></tr>
<tr><td>CON$_{(post)}$</td><td>70.5 ± 10.2</td></tr>
</table>

**Statistical significance*

A significant decrease ($p < 0.001$, CI = -2.1 ; -0.6) was noted in Table 4.9.1 when comparing the CON$_{(pre)}$ body mass 71.8 ± 10.1 Kg to the CON$_{(post)}$ body mass of 70.5 ± 10.2 Kg.

TABLE 4.9.2: WAIST GIRTH OF THE CON GROUP

Waist girth (cm)	$\bar{x}$ ± sd	p [CI]
CON(pre)	86.6 ± 8.7	0.161
CON(post)	85.8 ± 9.9	[-2.0 ; 1.5]

TABLE 4.9.3 HIP GIRTH OF THE CON GROUP

Hip girth (cm)	$\bar{x}$ ± sd	p [CI]
CON(pre)	83.9 ± 7.4	0.127
CON(post)	83.2 ± 7.6	[-0.5 ; 1.0]

TABLE 4.9.4 UPPER ARM GIRTH OF THE CON GROUP

Upper arm girth (cm)	Q_1	M	Q_3	p [CI]
CON(pre)	34.0	36.0	38.0	0.403
CON(post)	34.0	36.0	38.6	[-0.5 ; 0.5]

From Table 4.9.2 and 4.9.3 it can be seen that the waist-, hip-, and arm girth did not show significant changes from $CON_{(pre)}$ to $CON_{(post)}$.

TABLE 4.9.5: CALF GIRTH OF THE CON GROUP

Calf girth (cm)	$\bar{x}$ ± sd	p [CI]
CON(pre)	36.4 ± 3.4	0.001*
CON(post)	36.8 ± 3.6	[0.0 ; 1.0]

**Statistical significance*

In Table 4.9.5 however there was a significant increase ($p = 0.001$) from $CON_{(pre)}$ 36.4 cm to $CON_{(post)}$ values.

4.3.2 Vital signs from the CON group of participants

The vital signs presented in Table 4.10.1 below is again only from the CON-group of participants.

TABLE 4.10.1: SYSTOLIC BLOOD PRESSURE FOR THE CON GROUP

Systolic blood pressure (mmHG)	$\bar{x}$ ± sd	p [CI]
CON(pre)	142 ± 17	0.006*
CON(post)	135 ± 16	[-18 ; 0]

In Table 4.10.1 there was a significant decrease ($p = 0.006$) of 7mmHg in systolic BP from the $CON_{(pre)}$ mean of 142 ± 17 mmHg to the $CON_{(post)}$ value of 135 ± 16 mmHg.

TABLE 4.10.2: DIASTOLIC BLOOD PRESSURE FOR THE CON GROUP

Diastolic blood pressure (mmHG)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	82 ± 8	0.438
$CON_{(post)}$	80 ± 10	[-6 ; 2]

The diastolic mean in Table 4.10.2 however did not change significantly (p = 4.38) $CON_{(pre)}$ to $CON_{(post)}$.

TABLE 4.10.3: HEART RATE FOR THE CON GROUP

Heart rate (bpm)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	84 ± 17	0.007*
$CON_{(post)}$	76 ± 15	[-16 ; -1]*

Table 4.10.3 showed a significant decrease (p = 0.007 , CI = -16 ; -1) in pulse rate (PR) $CON_{(pre)}$ 84 ± 17 bpm to $CON_{(post)}$ 76 ± 15 bpm in the CON group.

4.3.3 Serum Calcium (Ca), Magnesium (Mg) and Phosphate (Ph) results in the CON group

The serum Ca, -Mg, and –Ph was taken additionally in the CON-group to help satisfy the aim of presenting a complete physiological profile of the participant population.

TABLE 4.11.1: TOTAL SERUM CALCIUM FOR THE CON GROUP

Total serum calcium ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	2.28 ± 0.09	0.001*
$CON_{(post)}$	2.38 ± 0.15	[-0.15 ; -0.04]*

TABLE 4.11.2: CORRECTED CALCIUM FOR THE CON GROUP

Corrected calcium ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	2.32 ± 0.09	0.294
$CON_{(post)}$	2.34 ± 0.12	[-0.43 ; 0.01]

In Table 4.11.1 above, the mean total serum calcium significantly increased (p = 0.001 , CI = -0.15 ; -0.04) $CON_{(pre)}$ 2.28 ± 0.09 $mmol.L^{-1}$ to $CON_{(post)}$ 2.38 ± 0.15 $mmol.L^{-1}$ whereas in Table 4.11.2 the corrected serum calcium did not show a significant change (p=0.294) from $CON_{(pre)}$ 2.32 ± 0.09 $mmol.L^{-1}$ to $CON_{(post)}$ 2.34 ± 0.11 $mmol.L^{-1}$.

TABLE 4.11.3: MAGNESIUM FOR THE CON GROUP

Magnesium ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	0.82 ± 0.09	1.000
$CON_{(post)}$	0.82 ± 0.10	[-0.03 ; 0.03]

The serum magnesium mean values remained similar $CON_{(pre)}$ 0.82 ± 0.09 $mmol.L^{-1}$ to $CON_{(post)}$ 0.82 ± 0.10 $mmol.L^{-1}$ (p=1.000) as seen in Table 4.11.3.

TABLE 4.11.4: PHOSPHATE FOR THE CON GROUP

Phosphate ($mmol.L^{-1}$)	$\bar{x}$ ± sd	p [CI]
$CON_{(pre)}$	1.08 ± 0.22	0.005*
$CON_{(post)}$	1.18 ± 0.18	[-0.17 ; -0.03]*

The serum phosphate values seen in Table 4.11.4 however also showed a significant increase (p = 0.005 , CI = -0.17 ; -0.03) from $CON_{(pre)}$ 1.08 ± 0.22 $mmol.L^{-1}$ to $CON_{(post)}$ 1.18 ± 0.18 $mmol.L^{-1}$.

4.4 CONCLUSION

Due to the large amount of data generated by the study, presented here in the tables above, the discussion of the results in Chapter 5, according to the literature, will be grouped into 4 main categories. These categories are chosen following the significant findings from the above mentioned tables. These categories are hydration, electrolyte disturbances, muscle damage and inflammation. The supportive findings in the discussion surrounding hydration are fluid intake, body mass, urea, creatinine, haemoglobin, haematocrit, protein, CO_2 and anion gap. For electrolyte changes the discussion will include findings on sodium, chloride, potassium, calcium, magnesium, phosphate. The factors for discussion surrounding muscle damage will be creatine kinase and myoglobin whereas for inflammation it will focus on the white cell count and lymphocytes.

CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

The information presented in Chapter 4 encompasses a brief overview of a mountain of data that was generated by this study. It affords also the opportunity for multiple follow-up studies. Chapter 5 will endeavour to answer the initial objectives posed in the presented protocol using only the mean or median values, depending on the data distribution, for the three groups i.e. $CON_{(pre),}$ $CON_{(post),}$ and CRA group. An in-depth analysis on an individual patient basis (although the ideal method) and attempt at explaining all of the findings will fall outside the scope of this particular study. The author also acknowledges the small CON group size due to the time constraints of the current study. Notwithstanding the before mentioned fact, an attempt will be made to generate "normal" or baseline physiological trends, in order to more meaningfully interpret the "cramp" or "abnormal" data trends later in this chapter as well as satisfy the aims of the study. The aims will be addressed and expanded on, and pitfalls dealt with as they present themselves. The aims will be grouped and presented in 2 major categories.

1. Formulation of a control or 'normal' profile of haematological and biochemical changes during a shift, in the mining population; and
2. Describing the prevalence and certain environmental, biochemical and haematological variables in gold miners working underground who present with exercise-associated muscle cramps (EAMC) at work.

A clear concern whilst considering the study participants and collected data is the presence of heat-related illnesses with cramping as a symptom or sign, as opposed to cramping related to the physical exertion and fatigue owing to the nature of the participants occupation. This study is concerned with the occurrence of cramping as the primary selective denominator for inclusion into the study (excluding the CON group). Observed cramping, as an entity, is the main focus. Description of physiological, haematological, and biochemical findings following the presentation of patients with observed cramping will be presented. A singular cause for the cramping, whether it be heat, fatigue, dehydration will not be preached, as the causative or priming mechanism is probably a combination of the factors that will be discussed here.

5.2 "NORMAL" HAEMATOLOGICAL AND BIOCHEMICAL CHANGES DURING A SHIFT IN THE MINING POPULATION

The objective of the CON group collection of data was twofold:

1. Formulation of a CON group of results, to which the retrospective data could be compared, as there were only post-event / shift blood results related to the patients presenting with cramps. It was felt that the "normal ranges" for blood results used in everyday practice was not adequate, in the target population being investigated due to the strenuous physical nature of their work, as well as the prevailing environmental conditions they are exposed to; and
2. The formulation of normative or reference data trends and the creation of a hypothetical "normal" biochemical and haematological profile for physical labourers working underground in South African gold mines.

Prior to embarking on the challenging task of describing a "normal" physiological, haematological, and biochemical model for employees working underground in one of the South African gold mines, a few acknowledgements regarding the limitations of the study will be made. The small sample size and a multitude of compounding variables that are present in the CON group of participants will challenge aspects of the findings. The full measure of the aim will thus not be satisfied, but rather diluted to a stimulus for further investigatory studies regarding the trends identified here.

Upon consultation with internal medicine specialists regarding the findings related to the CON group of patients, a few overall trends emerged. Some findings were consistent with our current knowledge, whereas others were more perplexing and warrant further investigation.

5.2.1 Hydration

The problem with the earlier studies in the mining population regarding hydration and cramping was that they did not monitor the hydration status and also did not have a CON group (Edsall, 1908; Talbot, 1935). This omission was addressed in this study.

Contrary to expectation, dehydration (specifically fluid volume loss) was not a common associated phenomenon affecting employees performing strenuous physical activity in the warm, humid environment that did not present with cramps. "Over-hydration", even if in a mild degree, seemed to be a common finding in the non-cramping- or CON group. This is in contrast to the findings in the CRA group. This will be expanded on in the section concerning the findings related to the cramp patients using the control findings as a baseline or normative data reference. The supporting factors emphasising the aforementioned include the following:

5.2.1.1 *Fluid intake and output*

Fluid balance would be difficult to interpret without looking at the amount of fluid taken during a shift and the weight before vs. after shift. Figure 4.1 showed that the majority of the CON group consumed between 0.40 – 0.59 $L.h^{-1}$ water during a shift. This would relate to between 2.4 L per shift and 3.54 L per shift. A significant decrease ($p < 0.001$, CI = -2.1 ; -0.6) was noted in Table 4.9.1 when comparing the $CON_{(pre)}$ body mass to the $CON_{(post)}$ body mass. There was a mean loss of 1.3 kg of body mass per 6 hours shift. This would point to quite a large amount of fluid loss during a shift (3.7 to 4.84 L mass or fluid loss (2.4 to 3.54 Kg plus the 1.3Kg)) being replenished with water only, as at the time of the study the employees were only allowed to take water and nothing more underground with them. The fluid loss through passing urine was not possible to calculate as it was not measured underground. However, the report from the CON group was that of either passing urine once or not at all.

5.2.1.2 *Haemoglobin and Haematocrit*

The haemoglobin and haematocrit in Tables 4.53 and 4.5.4 respectively, supports an increase in haemodilution in the CON group from $CON_{(pre)}$ to $CON_{(post)}$. This is evidenced by the CON group haematocrit (Hct) that showed a significant ($p = 0.001$) decrease in concentration from $CON_{(pre)}$ to $CON_{(post)}$. This was supported by the haemoglobin that showed a slight but statistically significant ($p=0.003$) decrease in the haemoglobin (Hb) concentration in the CON group $CON_{(pre)}$ to $CON_{(post).}$

5.2.1.3 *Urea*

The CON group in Table 4.7.1 showed a similar or slight but insignificant ($p = 0.438$) mean decrease in urea $CON_{(pre)}$ to $CON_{(post).}$ The important finding would rather be that there was not a significant increase in urea that could point to pre-renal dehydration in this CON group as a result of their underground work. This further does not oppose the over-hydration / haemodilution described at the hand of the Hb and Hct above.

5.2.1.4 *Creatinine and Glomerular Filtration Rate (GFR)*

Table 4.7.2 indicated that the $CON_{(pre)}$ mean serum creatinine showed a slight statistically significant ($p = 0.049$) increase to $CON_{(post)}$ values. This statistically significant finding however would not translate to a clinically significant increase in creatinine levels. This again supports the theory that the kidney's functioning, in the CON group, is not being over stressed and that the kidneys can cope well.

The median Modification of Diet in Renal Disease (MDRD) or Glomerular filtration rate (GFR) showed a slight but significant ($p = 0.003$) decrease $CON_{(pre)}$ to $CON_{(post)}$ in Table 4.7.6. The CON group participants, however, started the shift with a MDRD / GFR level below the normal reference value of >90 $ml.min^{-1}$. GFR is an indicator of renal function (Levey *et al,* 1999). GFR reported by the lab uses the disputed method that was developed by the Modification of Diet in Renal Disease Study Group (MDRD) which estimates GFR using four variables: serum creatinine, age, ethnicity, and gender. Creatinine is a by-product of muscle metabolism that is excreted unchanged by the kidneys. Increase in creatinine levels is thus also related to increase in production of creatinine through muscle breakdown due to starvation and physical activity or exertion during a shift and not only due to the decreased GFR (Baird, 2012). Due to MDRD method for calculating the GFR, it would follow that an increase in serum creatinine due to increased muscle metabolism could cause a false decreased GFR.

5.2.1.5 *Total serum protein*

From Table 4.6.1 it can be seen that the Total protein values showed an insignificant ($p = 0.004$) increase from $CON_{(pre)}$ to $CON_{(post)}$ in the CON group. This small increase when considered in isolation again would not be a clinically significant finding. When relating the total protein in Table 4.6.1 to the serum albumin in Table 4.6.2, there was a concomitant significant ($p < 0.001$, CI = 1.0 ; 4.0) increase in mean serum albumin levels $CON_{(pre)}$ to $CON_{(post)}$ in the $CON_{(group).}$ With the 3.6 $g.L^{-1}$ increase in the total protein $CON_{(pre)}$ to $CON_{(post)}$ one can see from the concomitant 3.1 $g.L^{-1}$ increase in the albumin contribution that the increase in total protein was as a result of an increase in albumin.

The increase in protein concentration (even if small) in Table 4.6.1 is not expected with the prevailing haemodilution picture as evidenced by the decreased haemoglobin and haematocrit. In normal circumstances, haemodilution would also be expected to dilute the protein concentration as well, as the amount of circulating protein tends to stay constant (Myhre & Robinson, 1977). The main contributor, in this study, to the increase in protein is the relative increase in albumin (vs. globulin contribution). Albumin is the main protein of human plasma. The albumin gene family consist of human serum albumin (50%), Vitamin D-binding protein and alpha-fetoprotein. It binds water, cations (such as Ca^{2+}, Na^{+} and K^{+}), fatty acids, hormones, bilirubin, thyroxine (T4) and pharmaceuticals. Its main function however is colloid osmotic pressure. An increase in serum albumin could lead to intra-cellular dehydration that forms part of the dehydration model presented in chapter 2. In episodes of starvation Albumin is also not catabolised and will thus increase the serum concentration (Birn, 2006). At the time of this study the mine workers were only allowed to take water underground but not food, so they were at the end of a shift physiologically entering a starvation state and that may have caused the relative increase in protein, specifically the albumin. Vitamin D binding protein transports Vitamin D to tissues. Due to the patients' lack of exposure to sunlight, this could possibly increase the Vitamin D binding protein expression and thus the albumin concentration. The author could unfortunately not find any studies that could concur or disagree with this statement.

5.2.1.6 *Electrolyte changes*

Potassium

A discussion regarding the potassium results are withheld in this study as there was concern of haemolysation in some of the specimens, and as such the results may be subject to an abnormal increase in serum potassium. The specimens were handled according to the proper cold chain technique and as such the significance of this haemolysation is unknown at this time. The reports of haemolysation from the lab was almost exclusively related to the pre-shift specimens that was kept in the fridge at 4°C to be delivered to the lab with the post-shift specimens after the shifts.

<u>Sodium (Na)</u>

The serum sodium levels in Table 4.7.3 showed a slight but significant ($p = 0.012$) decrease $CON_{(pre)}$ to $CON_{(post)}$. This could support a haemodilutional decrease in serum sodium concentration due to the high water intake and resultant fluid losses (5.2.1.1), that would again link with the decrease in Hct (Myhre & Robinson, 1977), or possibly a net loss of sodium in sweat in the CON group.

<u>Chloride (Cl)</u>

As seen in Table 4.7.4, serum chloride showed a small statistically significant ($p < 0.001$, CI = -4 ; -1) decrease $CON_{(pre)}$ to $CON_{(post)}$ in the CON group. This decease again could accompany a haemodilutional picture in the CON group of participants or possibly a net loss of chloride in sweat in the CON group (Shearer, 1990).

5.2.2 Muscle damage or breakdown

5.2.2.1 *CK levels*

As expected Table 4.8.1 showed that after a shift of hard physical labour, the median $CON_{(pre)}$ creatine kinase level is followed by a significant ($p < 0.001$, CI = 21 ; 66) increase in the creatine kinase level in the $CON_{(post)}$ results. This is due to muscle breakdown or rhabdomyolysis associated with strenuous physical exertion (Olerud, *et al.*, 1976; Knochel, 1990). It is important to note that the average pre-shift CK was already high. The CON group of participants were tested on Wednesdays thus it could show that the CK was accumulating with consecutive shifts, indicating insufficient recuperation time between shifts. A possible reason for this accumulation that one sees is the fact that CK (due to its large molecular size) is transported in the lymphatic system and thus takes longer to clear from the body (Senert, *et al.*, 1994).

5.2.2.2 *Myoglobin*

Similarly to the CK levels, the mean $CON_{(pre)}$ myoglobin in Table 4.8.2 showed a small but still significant (CI = 4.0 ; 26) increase in the $CON_{(post)}$ results. This statistically significant increase, however, is still within the normal reference ranges for serum myoglobin unlike the case with the creatine kinase values above. This would indicate that myoglobin levels do not exceed normal physiological levels during a normal shift.

5.2.3 Muscle fatigue

5.2.3.1 *Creatinine*

As mentioned in the hydration section (cf. Section 5.2.1.4) above, creatinine is a by-product of muscle metabolism that is excreted unchanged by the kidneys. Thus the reason for the increased creatinine (cf. Table 4.7.2) in the face of evidence pointing to haemodilution (decreased Hb and Hct), could be through the increased physical exertion in the presence of relative starvation (as mentioned above) as well as a slight decrease in GFR of creatinine through the kidneys (Baird, 2012).

5.2.3.2 *Serum CO_2*

The CO_2 in Table 4.7.7 did not show a significant ($p = 0.881$) increase from $CON_{(pre)}$ to $CON_{(post)}$ in the CON group. Increased work increases the production of CO_2 as a by-product of cellular metabolism. The similar results in the $CON_{(pre)}$ to $CON_{(post)}$ group is expected in healthy individuals performing physical labour as they are able to control the CO_2 serum concentration by exhaling excessive CO_2 and physiological buffering (Centor, 1990).

5.2.3.3 *Creatine kinase (CK)*

The presence of a raised CK level in the $CON_{(pre)}$ group pre-shift already, increasing to the $CON_{(post)}$ post-shift results in Table 4.8.1 without a concomitant rise in myoglobin, may point to another speculative mechanism for the increase in CK levels. Please see the discussion regarding muscle fatigue in section 5.3.2.3 below dealing with the CRA vs. $CON_{(post)}$ groups under the heading of muscle fatigue.

5.2.3.4 *Glucose*

As seen in Table 4.7.9 above, the serum glucose mean value showed a small but significant (p = 0.012 , CI -0.2 ; -1.3) decrease in the $CON_{(pre)}$ to $CON_{(post)}$ group values. At the time of the study, workers were also not allowed to take food or glucose-containing drinks underground.

5.2.4 Inflammatory response

5.2.4.1 *White cell count (WCC)*

The $CON_{(post)}$ group displayed a median WCC following their work shift which was slightly yet significantly higher (p = 0.026) than the $CON_{(pre)}$ WCC before their work shift which fits in with our understanding of WCC responses to exertion (Galun, *et al.*, 1987) . Although it is a small increase, it is mentioned here to establish a proper baseline or "normal" picture for physical labourers working underground. The CON group presented with a lymphocyte concentration before their work shift, which increased significantly (p = 0.044) directly after their work shift. The increase in concentration of serum lymphocytes was responsible for ±50% of the increase in serum WCC. This is again mentioned here to compare with the discussion regarding the changes seen in the CRA group below. There was an interesting finding in one of the rock driller participants who presented with an initial raised eosinophil count pre-shift of 0.737 x $10^9.L^{-1}$. This reduced quite dramatically during shift to a post-shift level of 0.466 x $10^9.L^{-1}$.

5.2.5 Other findings

5.2.5.1 *Vital signs*

When looking at the CON group the effect of the physical exertion seemed mainly to affect the systolic BP. In Table 4.10.1 there was a significant decrease (p = 0.006) of 7mmHg in systolic BP from the $CON_{(pre)}$ mean of 142mmHg ± 17 mmHg to the $CON_{(post)}$ value of 135mmHg ± 16 mmHg whereas the diastolic mean in Table 4.10.2 did not change significantly (p = 4.38) $CON_{(pre)}$ to $CON_{(post)}$ (Thompson, *et al.*, 2001).

Table 4.10.3 showed a significant decrease ($p = 0.007$, CI = -16 ; -1) in pulse rate (PR) $CON_{(pre)}$ 84 bpm ± 17 bpm to $CON_{(post)}$ 76 bpm ± 15 bpm in the CON group. The significance of this significant decrease is unknown (Thompson, *et al.*, 2001).

5.2.5.2 *Calcium, Magnesium and Phosphate*

The calcium, magnesium and phosphate levels pre- and post-shift was included in the CON-group as the aim was to establish a baseline / "normal" physiological picture in physical labourers working underground. The absences of these blood parameters in the CGR-group make speculation on possible findings in the CRA-group immature. In the study by Shearer (1990), the corrected values at day zero (incident / cramp date) saw a decreased calcium (6%) and phosphate (5%) when compared to day seven post-incident (i.e. the normal values). Magnesium, however, was 13% higher on day zero (incident date) than on day seven post-incident indicating that there was a higher serum concentration of magnesium on the incident day.

Due to the absence of these results in this study in the CRA group, the CON group findings will be presented here so future follow-up studies can have a normal baseline to compare to results in patients presenting with cramping in the underground mining population.

Calcium (total and corrected)

In Table 4.11.1 above, the mean total serum calcium significantly increased ($p = 0.001$, CI = -0.15 ; -0.04) $CON_{(pre)}$ to $CON_{(post)}$ whereas in Table 4.11.2 the corrected serum calcium did not show a significant change ($p = 0.294$) from $CON_{(pre)}$ to $CON_{(post)}$. This increase is in contrast to the expected hypocalcaemia described by Sprung *et al.* (1980) and Lampetro (1963) following exertion in heat. Owing to the picture of relative over-hydration seen in the CON group, hypocalcaemia might still be the case (Shearer, 1990)
Calcium has an integral role in the physiology and biochemistry of various cells and is one of the most closely regulated elements in the body (regulated within 1-2% changes), so even small changes may be of value. It plays an important role in signal transduction pathways, where it acts as a second messenger; in neurotransmitter release from neurons; and contraction of all muscle cell types. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes. The physiology of calcium is very complex and falls outside the aims of the current study. It is felt that

the further investigation, especially the comparison of this baseline to cramping patients, would be of great value.

Magnesium

The serum magnesium mean values remained similar $CON_{(pre)}$ to $CON_{(post)}$ (p = 1.000) as seen in Table 4.11.3. Magnesium is a common element prescribed in the management or prevention of cramping and as such, it would be worth investigating in the patients who present with cramps, to compare to this baseline. In the Shearer (1990) study, he found that on the day of the incident (heat that presented with cramps) the serum magnesium was actually 13% higher when corrected for haemoconcentration (dehydration). This might warrant further investigation especially seeing as how magnesium is commonly advised in people who suffer from cramping.

Phosphate

Phosphate has been found to be raised in heat exhaustion (Leithead & Lind, 1964) and lowered in heat stroke (Sprung, *et al.*, 1980). In this study the serum phosphate values seen in Table 4.11.4 showed a significant increase (p = 0.005 , CI = -0.17 ; -0.03) from $CON_{(pre)}$ to $CON_{(post)}$, thus similar to the findings by Leithead and Lind (1964) in heat exhaustion patient. Phosphate has important functions in pH regulation in the body. It must be reiterated that the value in having this baseline would be the comparison to CRA-group patients.

5.2.5.3 *Liver functions*

Serum liver function tests gives information on both the serum tubular enzymes (ALP, GGT) as well as the cellular enzymes (ALT, AST). Even though the liver function results did not show clinically significant changes, the test results are mentioned here for completeness and as part of the formulation of a "normal" physiological profile in physical labourers working underground. Unlike the other hepatic enzymes, although not considered as clinically significant, ALP (cf. Table 4.6.3) did show a statistical significance (p = 0.012) decrease from $CON_{(pre)}$ to $CON_{(post)}$. In Tables 4.6.4, 4.6.5, and 4.6.6 the serum GGT ALT and AST respectively did not show a significant change $CON_{(pre)}$ to $CON_{(post)}$.

5.2.6 Summary of Section 5.2

"Formulation of a control or 'normal' profile of haematological and biochemical changes during a shift, in the mining population".

This underground mining employee, performing physical labour in a hostile (hot and humid) environment without developing EAMC is an individual with the following traits:

- A man or woman that is a well to slightly over-hydrated
- Present with progressive muscle injury (increased CK levels, but no increase in myoglobin) during a working week
- Experience muscle fatigue with a slight WCC reaction as a result of his daily labours
- Work in cramped spaces with heavy and sometimes vibrating tools or who walks long distances or stands for long periods of time
- Regulates his or her body temperature and homeostasis with minimal stress on their liver and kidneys when acclimatised.

5.3 ENVIRONMENTAL, BIOCHEMICAL AND HAEMATOLOGICAL VARIABLES IN GOLD MINERS WORKING UNDERGROUND WHO PRESENT WITH EXERCISE-ASSOCIATED MUSCLE CRAMPS (EAMC) AT WORK

The cramp-group findings will be presented as averages to form a global perspective of the physiological changes associated with cramping in the mining population. A further more intensive, in-depth investigation, considering the participant results (and interplay of results) on an individual basis, will be of further value but falls outside of the scope of this particular study aims.

5.3.1 Environmental and occupational findings

5.3.1.1 *Day of the week*

The occurrence of cramping showed a definite predilection for Tuesdays (28%) and Wednesdays (25%) as seen in Table 4.1. Anecdotally, the cramping incidents that peaked on Tuesdays and Wednesdays, did so following "on-weekends" (working weekends including Saturday and Sundays) which in essence meant that the cramping peaked at days 8 and 9 working (as opposed to a Monday to Friday work week).

5.3.1.2 *Occupational*

As explained in Chapter 3 (cf. 3.3.3), a decision was made to organise participants into groups comprising employees engaged in occupations with similar levels of physical exertions (thus exposed to the same physical requirements). The occupations were organised according to the level of exertion (high intensity or low intensity) and furthermore whether the exertion was performed in a more static position or under more dynamic circumstances. This decision was made following consultation with various occupational health practitioners and occupational therapists working in the mining sector. A fairly diverse representation of workers with relation to their occupations was obtained for the formulation of the CON group. The two groups (CRA and CON-group) did not significantly differ ($p = 0.270$) in participant make up. From Table 4.2 it can also be seen in the CRA group that, when combining the incidence of cramps in the Static occupations (Static high intensity + Static low intensity) it amounts to 63.97% of the cramping incidence versus the 36.04% when combing the dynamic occupations (Dynamic high intensity + Dynamic low intensity). The majority of the cramping incidence in the Static group was in the group: Static, high intensity (38.74%).The occupational distribution regarding the CON group showed a similar pattern to the CRA group distribution, where 64.52% fell in the static groups. This similarity in the makeup of the CON- and CRA group helps with drawing comparisons between findings.

Furthermore, there are 4 main types of physical stresses on the employees depending on their designations:

1) Vibration

   This occurs in the drillers. However they are exposed to this vibration whilst in a cramped position (squatting, sitting etc.) depending on the height of the area they work in.

2) Cramped position for prolonged periods

   This group would include Winch operators (less physical exertion) and the drillers and stoppers (More physically active).

3) Hard physical exertion

   The stope team and development team perform heavy physical labour (cf. section 2.4.2.2.

4) Distance walking

   This group consisted of the miners' assistants as explained in section 2.4.2.4.

   The vast majority of patients that are affected by cramps are the rock drillers (35.4%). They perform heavy physical labour with vibrating tools in squatting positions. The stope team members (15.4%) also work in confined spaces whilst performing heavy physical labour. The winch drivers (18.9%) on the other hand perform their duties - which are of a less physical nature - for protracted periods of time in a fixed flexed position. The use of the term EAMC in this specific group of employees (winch drivers) according to the definition EAMC: "painful, spasmodic and involuntary contraction of skeletal muscle that occurs during or immediately after exercise" (Schwellnus, 2009) seems problematic as evidenced by the job description presented in section 2.4.2.3. This should, even more, so highlight the complexity when examining the aetiology of the entity of cramping.

5.3.1.3 ***Environmental***

<u>Heat & Humidity</u>

In a related study concerning 35 of 52 heat-related illness patients (diagnosed as having a heat related illness) presenting complaints was cramps (Shearer, 1990). It is thus very difficult to completely separate the phenomena of cramping from an association with heat. In this study, Table 4.4 shows that the CON group displayed similar (p = 0.144, CI = -0.2 ; 0.7) body temperatures before (M = 36.0°C) and after (M = 36.2°C) their work shift. When comparing the $CON_{(post)}$ and $CRA_{(post)}$ group data, significantly higher (p = 0.001, CI = 0.2 ; 0.6) body temperatures were seen for the CRA group. There are a few limitations to the interpretation or acceptance of the CRA group temperature in this study.

They are:

1) Temperature was measured by different staff at different venues and the quality and reproducibility of the readings can't be verified.
2) The staff taking the temperature mostly used tympanic thermometers and proper rectal temperatures were only taken once the patient reached casualties.
3) As part of the procedure at the mine concerning patients presenting with cramps, the following is performed. When a person presents with cramping, they are removed from the hot area, wet with water and then an air-jet is used to blow air over them in order to cool them down. This happens due to the fear of heat illness. Thus, when the patient reaches surface he has been preventatively cooled down a lot.

Humidity plays an important role in the body's ability to regulate hydration and dissipate heat produced through increased metabolism, through the production of sweat. Anecdotal observations, as mentioned multiple times, still show that when a rise in ambient temperature occurs underground (especially when associated with a high humidity), we prepare to receive patients with cramping.

Air pressure

Many physics laws are possibly at work on the employees working underground, and the effects of this "high pressure" environment have not been well documented. The area where the tests were performed was 1 376m above sea-level. Some of the shafts are up to 3km underground and the employees travel this distance in a couple of seconds before starting their physical occupations. As such, some of the following laws may become relevant. Possible applicable laws may include amongst others, Henry's law. It states: "At a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid." The significance of these effects is unknown and speculation falls outside the scope of this study but could warrant further investigation or at the least consideration when interpreting data in the mining population.

5.3.2 Haematological and biochemical findings

Multiple grouping options were available to further extrapolate or highlight prevailing trends related to a certain parameter, for example using myoglobin as the main group selector, and then studying the trends that ensue in the other biochemical findings after the grouping of cramp cases from a low to high myoglobin. Due to the large amount of data produced in this particular study, we will use CON- and CRA group averages only.

The same identified overall themed trends as for section 5.2 above (CON-pre vs. CON-post) was again observed and used to expand on in this section (CRA vs. CON-post). No conclusions will be presented as fact here. Loose associations will rather be highlighted in order to stimulate further studies or investigation.

5.3.2.1 *Hydration (Dehydration)*

As opposed to the $CON_{(post)}$ group, the CGR group showed signs of dehydration. The findings in the $CON_{(post)}$ group indicated the presence of proper, if not "over-hydration". A comparison of the $CON_{(post)}$ versus the result of the CRA group will be presented below.

i) Haemoglobin (Hb) and Haematocrit (Hct) (cf. Tables 4.5.3 & 4.5.4)

The haematocrit as discussed above decreased in the CON group pre- to post-shift pointing to haemodilution. When comparing the CRA with the $CON_{(post)}$ values, the CRA group had a median Hb measurement which was significantly higher ($p < 0.001$, CI = 1.1 ; 2.3) compared to the $CON_{(post)}$ Hb measurement as well as an accompanying significantly higher ($p < 0.001$, CI = 0.03 ; 0.06) Hct when comparing the $CRA_{(post)}$ Hct to the $CON_{(post)}$ Hct concentrations. Even though there were no pre-shift Hct available for the CRA group, the difference between the mean CRA and $CON_{(post)}$ group is marked and would suggest a degree of haemoconcentration (dehydration). Thus it will appear that haemoconcentration may play a role as an associated risk / predisposing factor.

ii) Urea (cf. Table 4.7.1)

The mean serum urea value in the CRA group showed a significantly higher value ($p < 0.001$, CI = 2.0 ; 3.8) compared to the $CON_{(post)}$ values. An increase in urea is associated with the increased oxygenation of protein (from muscle breakdown) and pre-renal dehydration (Hediger *et al.,* 1996). Thus the lower levels of urea in the CON-post group may also be a sign of a smaller degree of muscle breakdown in these non-cramping patients and not only be related to the hydration status. Urea levels may however be affected by factors like diet as well. Diet as a major contributing source of protein is however not likely in this particular population as their diet mainly consists of starches. In future studies it will be of value to add a urine urea concentration to better understand the function of ADH (anti-diuretic hormone) in this population as ADH is a major player in fluid balance (Hediger *et al.*, 1996).

iii) Creatinine (cf. Table 4.7.2) and GFR (MDRD) (cf. Table 4.7.6)

The CRA values showed a significantly ($p < 0.001$, CI = 35 ; 99) higher mean value than the $CON_{(post)}$ values. The CRA median MDRD/GFR showed a significantly ($p < 0.001$, CI = -43 ; -18) lower value when compared to the $CON_{(post)}$ mean in the CON group. When using the MDRD method (as was done in this study), in the presence of a factor that can increase the production of creatinine (increased physical labour), you could expect a misleadingly low GFR as is the case here in the CRA and above in the CON group.

iv) Total protein

In the CON group the increase in the total protein $CON_{(pre)}$ to $CON_{(post)}$ with its concomitant similar $g.L^{-1}$ increase in the serum albumin concentration showed that the increase in total protein increase was as a result of an increase in albumin.

When comparing the $CON_{(post)}$ group to the CRA however, the CRA shows a significantly higher total serum protein $CON_{(post)}$ vs. CRA ($p < 0.001$, CI = 6 ; 15). Comparing the $CON_{(post)}$ group to the CRA group, the CRA group shows a significantly higher mean Albumin serum content $CON_{(post)}$ vs. CRA ($p = 0.005$, CI = 2.0 ; 7.0). The percentage contribution of albumin to the higher total protein was at roughly 50% in this group. The percentage contribution of albumin to the total serum protein in the $CON_{(post)}$ group is 51.62% that is thus a similar contribution of serum albumin to the total serum protein in the CRA group of 50.38%. The normal expected contribution of serum albumin to total serum protein is between 55 and 60% (Birn, 2006).

The CON group showed a slight increase in total serum protein in the $CON_{(pre)}$ to $CON_{(post)}$ group. As mentioned above in the discussion on the CON group findings, this increase in protein concentration is not expected with haemodilution evidenced by the decreased haematocrit as in normal circumstances, haemodilution would also be expected to dilute the protein concentration (Ohira, *et al.*, 1977). The CRA group mean, however, showed a markedly higher protein concentration compared to the $CON_{(post)}$ group. This fits in with a dehydration or haemoconcentration picture in the CRA group when compared to the $CON_{(post)}$ group (Ohira, *et al.*, 1977).

The main contributor, in this study, to the increase in protein was the relative increase in albumin (vs. globulin contribution). Albumin is the main protein of human plasma. The albumin gene family consist of human serum albumin (50%), Vitamin D-binding protein and alpha-fetoprotein. It binds water, cations (such as Ca2+, Na+ and K+), fatty acids, hormones, bilirubin, thyroxine (T4) and pharmaceuticals. Its main function however is colloid osmotic pressure. Serum albumin is known to increase due to diet, dehydration (decreased renal perfusion) and increased tourniquet time when taking the blood sample (Birn, 2006).

An increase in serum albumin could lead to intra-cellular dehydration that forms part of the dehydration model presented in chapter 2 (cf. 2.2.1). In episodes of starvation Albumin is also not catabolised. At the time of this study, the mine workers were only allowed to take water underground but not food, so they were at the end of a shift physiologically entering a starvation state and that may have caused the relative increase in protein, specifically the albumin. Vitamin D binding protein transports Vitamin D to tissues. Due to the patients' lack of exposure to sunlight, this could theoretically increase the Vitamin D binding protein expression and thus the albumin concentration (Birn, 2006).

v) Electrolytes

Sodium & Chloride

As discussed in chapter 2 (cf. 2.1), sodium and chloride plays a central role in the dehydration and disturbed electrolyte hypothesis (salty sweaters) (Bergeron, 2008; Eichner, 2007; Stofan, *et al.*, 2005). The mean serum Na values for the $CON_{(post)}$ group and the CRA group did not show a significant difference ($p=0.232$) when considered in isolation (cf. Table 4.7.3). The study by Shearer (1990) showed that when you correct for haemoconcentration (dehydration) using either of the two described methods, serum total protein (Ohira *et al.*, 1977) or Hb / Hct (Dill and Costill 1974) you have a very hyponatraemic or sodium depleted (mean of up to 105.6mmol.L-1) picture of patients presenting with cramps. This is compared to the relatively constant uncorrected sodium values in the same patients presenting with cramps. Thus, the sodium level in the CRA would most likely also be a lot lower if you were to correct for the haemoconcentration as evidenced by both the Hb/Hct and serum protein levels. Higher fluid intake was also associated with lower corrected Na levels (dilutational hyponatremia) (Shearer, 1990).

In Table 4.7.4 there was a significantly (p=0.026) lower mean when comparing the CRA values to the $CON_{(post)}$ group values. Thus, the chloride levels in the CRA group did not follow that of the sodium serum concentration (which showed a slight but statistically insignificant increase in serum concentration). Sodium physiology is, however, very complex and changes in concentration could be associated with the renin-angiotensin system, Na/K-ATPase, haemodilution, haemoconcentration, increase in serum albumin levels binding the cations like sodium; thus, for the purposes of this study, no further speculation will be presented here.

vi) Fluid balance

With the CRA group no pre-cramp (or shift) nor post-cramp (or shift) information on body weight is available. This makes it very difficult to properly interpret the findings on hydration status and further studies will thus be needed, as the results presented is merely a description of the findings the study did produce.

5.3.2.2 *Muscle damage / breakdown*

As mentioned in section 2.3.2, cramping often accompanies, or is an early sign or symptom of rhabdomyolysis (Moeckel-Cole & Clarkson, 2009; Anzalone, *et al.*, 2010; Clarkson & Sayers, 1999; Cleary, *et al.*, 2007) Rhabdomyolysis again is often a complication of strenuous physical exertion and as such there seems to be a link or at the least an association between strenuous exercise / physical exertion, rhabdomyolysis and cramping.

CK levels (cf. Table 4.8.1)

With interpretation of CK levels in the CRA group, one needs to keep in mind the findings of the CON group that showed a higher CK serum mean pre-shift already, possibly indicating a cumulative increase in CK levels during a working week. Thus when you look at the CK levels in the CRA group, when compared to the $CON_{(post),}$ it did not show a significant change (p = 0.222). Two problems now arise:

1) Even though the more than 50% of cramp cases occurred either on Tuesday or Wednesday, the CRA group average would still be comprised of CK levels post-cramping on other days of the week. With no pre-shift CK level, the combined mean total serum CK values will negate the fact that there seems to be a cumulative nature of CK levels as the work week progresses; and
2) No CK-MB results are available for the CRA group.

If we were to only use the employees that cramped on Wednesdays' (same day as the tests for the whole CON group) average CK level 685.45 u.L-1 37°C to compare to the $CON_{(post)}$ value mean 360 ± 235.4 u.L-1 37°C you see a greater difference than when comparing the CRA total median of 331 units.L^{-1} 37°C to the CON post group. When you do look at the average CK levels for CRA participants on consecutive days, a trend also emerges. The average CK in patients that cramp on Mondays is 276.31u.L-1 37°C, on Tuesdays 461.54u.L-1 37°C, on Wednesdays 685.45u.L-1 37°C, Thursdays 610.77u.L-1 37°C, Fridays 660.91u.L-1 37°C. This may well point to the fact that the cramping in itself is not such a big contributing factor to the higher CK levels found in cramping patients as previously thought (Senert, *et al.*, 1994).

The controversy that however remains, when considering CK-levels and cramping, is whether the cramping only increases the CK during an episode, or to what degree the cramping may be as a result of the increased in muscle damage as evidenced by the increase in CK.

<u>Myoglobin levels (Table 4.8.2</u>)

As mentioned above, the mean $CON_{(pre)}$ myoglobin in Table 4.8.2 only showed a small but significant (CI = 4.0 ; 26) increase in the $CON_{(post)}$ results. Myoglobin did show a significantly higher ($p < 0.001$, CI = 66.0 ; 230) value when comparing the mean CRA to the $CON_{(post)}$ group. Myoglobin is only found in the bloodstream after muscle injury (rhabdomyolysis) and is thus an abnormal finding that is diagnostically relevant when found. This makes it a sensitive marker for muscle damage (Knochel, 1990). Myoglobin itself is not as toxic as it is a protoxin. It is the ferrihemate portion that is dissociated from myoglobin in acidic environments (e.g., acidic urine, lysosomes) that is nephrotoxic. This nephrotoxicity makes myoglobin levels an important consideration in the management of patients with severe cramping.

It is not possible, from this study, to say that a raised myoglobin level is solely the result of cramping. Two opposing arguments can be presented.

1) As the CON group (except for one participant) showed no significant increase in myoglobin pre- to post-shift, the cramping must have caused the increased tissue damage and subsequent rise in myoglobin;
2) On the other hand, the CRA group did not have a pre-cramping / pre-shift battery of baseline blood results with which to compare, so they may have had a raised myoglobin level due to the nature of their occupational physical requirements leading to a cramping episode; and
3) There is, however, a third option also: The patient may have developed progressive muscle damage during a shift without it progressing to full cramping. An individual threshold may then be reached where the patient will progress to generalised cramping with progressive or continued muscle damage (increase in serum myoglobin).

<u>Myoglobin and CK</u>

The discourse in the myoglobin CK relationship could possibly indicate a different reason for the sequential increase in CK during a working week, seeing as to how the myoglobin levels does not support muscle damage (rhabdomyolysis) as a the only source for the sequential increase in CK. Please see muscle fatigue topic below for more on the CK levels.

<u>Urea</u>

The higher serum urea levels seen in the CRA when compared to the $CON_{(post)}$ group may be evidence, in part, of increased muscle breakdown seen in the CRA group.

5.3.2.3 ***Muscle fatigue***

In the mining sector, since the advent of formal acclimatisation strategy, there has been a greatly decreased incidence of heat stroke and related episodes of cramping. This would indicate that, reducing the fatigability of muscles and aiding in a gradual exposure to the combination of physical exertion in adverse environmental conditions (heat and humidity), by acclimatisation exercises, helps reduce the incidence of cramping and heat-related illnesses (Strydom, *et al.*, 1975). Other factors that may also help support the muscle fatigue theme in the study results are the following:

Creatinine

As mentioned under the hydration topic, and further as seen in Table 4.7.2 the CRA values showed a significantly ($p < 0.001$, CI = 35 ; 99) higher mean value than the $CON_{(post)}$ values. As discussed under hydration Section 5.3.2.1, a contributory factor to an increase in creatinine levels could be increased muscle metabolism or muscle work seeing that creatinine is a by-product of muscle metabolism (Baird, 2012). When using the MDRD method (as was done in this study), in the presence of a factor that can increase the production of creatinine (increased physical labour), you could expect a misleadingly low GFR. This indirectly (to a degree) could indicate an increased work load and thus an increased level of fatigue in the CRA group.

Serum CO_2 (Table 4.7.7)

The CO_2 in Table 4.7.7 did not show a significant ($p = 0.881$) increase from $CON_{(pre)}$ to $CON_{(post)}$ in the CON group as expected due to the regulation of CO_2 mainly by exhaling excessive produced CO_2 (Baird, 2012). However, when you compare the mean CRA values to the mean $CON_{(post)}$ value, the CRA values showed a slight but significantly lower mean value ($p < 0.001$, CI = -3.0 ; -0.9). CO_2 is measured instead of bicarbonate. The total CO_2 content includes the serum bicarbonate plus other available forms of carbon dioxide (dissolved CO_2 and carbonic acid). Generally, as much as 95% of the serum bicarbonate is made up by the total CO_2 content; thus, we can use this measurement as an excellent estimator of serum bicarbonate (Centor, 1990). The reason for the lower mean serum CO_2 concentration in the CRA group, even if small, is not clear. There several possibilities though, hyperventilation probably being the most likely. Reasons for hyperventilating can include amongst others, performing work above VO_2max for periods of time, where they are unable to generate sufficient energy through purely aerobic respiration, but then hyperventilate in an effort to do so. A low partial pressure of carbon dioxide in the blood also causes alkalosis, leading to lowered plasma calcium ions and increased nerve and muscle excitability. This could explain the other common symptoms of hyperventilation — pins and needles, muscle cramps and tetany in the extremities, especially hands and feet.

Thus it would have been especially interesting to have had the pre- and post-cramp calcium values.

Interestingly, when considering some of the cramp patients with very high myoglobin levels individually, the CO_2 seems to go quite low for ex. 15-16mmol.L^{-1}.

Creatine kinase (CK)

CK is an enzyme that is expressed by various tissues and cell types and catalyses the conversion of creatine while consuming adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and thus ATP can be generated from PCr and ADP. In tissues and cells that consume ATP rapidly, especially skeletal muscle, PCr serves as an energy reservoir for the rapid buffering and regeneration of ATP in situ, as well as for intracellular energy transport by the PCr shuttle or circuit. Thus creatine kinase, being an enzyme, should have the possibility or ability of being up-regulated as with other enzymes when needed as would be the case with high levels of physical exertion on consecutive working days. This could then possible explain the sequential increase in CK during the week (Senert, *et al.*, 1994).

5.3.2.4 *Inflammation*

The inclusion of the topic or category of inflammation is controversial. The controversy would be whether the cramping, especially when severe, causes or at the very least contributes to presence of an inflammatory response through muscle damage, or if the evidence for an immune response to an underlying illness contributed to the development of the cramps. Either way, the haematological findings will be presented here as a leukocytosis and neutrophil activation were postulated to accompany short- (even within two hours of exercising (Biondi, *et al.*, 2003) and medium-length exercise but studies have shown this especially during and following prolonged exercise (Biondi, *et al.*, 2003). Prolonged or short intense bouts of exercise or exertion are associated with exertional rhabdomyolysis which in turn is associated with cramping (Moeckel-Cole & Clarkson, 2009; Anzalone, *et al.*, 2010; Clarkson & Sayers, 1999; Cleary, *et al.*, 2007).

White cell count

The $CON_{(post)}$ group displayed a median WCC following their work shift which was slightly yet significantly higher ($p = 0.026$) than the $CON_{(pre)}$ WCC before their work shift. The CRA group presented with a median WCC, when presenting to the medical centre with EAMC during or after a shift, which was significantly higher ($p < 0.001$) compared to the WCC of the $CON_{(post)}$ group following a work shift.

The argument that arises here is: What percentage does the following two aspects contribute to the higher mean WCC in the CRA group:

1) Pre-existing infection. In other words, did the patients who presented with cramping have an existing infection, prior to the shift where they developed cramps? Thus does an underlying infection predispose to developing cramps as is widely thought? OR
2) Immune reaction to increased muscle damage. In other words, did a progressive increase in muscle damage leading to cramping cause an inflammatory response? In a study tracking muscle injury and white cell response in 1987 during a 16 hour march, Galun (1987) found a parallel increase in plasma creatine kinase activity from 127 ± 4.4 $u.L^{-1}$ to 539 ± 106.3 $u.L^{-1}$ ($P < 0.001$), indicating muscle cell damage and also an accompanying increase in WCC (Galun, *et al.*, 1987); and
3) All the white cell types are given as a percentage and as an absolute number per litre. WCC consists of the total combined number of lymphocytes, neutrophils, basophils, eosinophils and monocytes in varying percentages. The major contributors to the WCC however are the lymphocytes and neutrophils.

In table 5.1 below the WCC contributors are broadly examined. As information was not gathered on the WCC differential count in the CRA group, except for the lymphocytes, the lymphocytes contribution will be expressed as a percentage of the WCC for further discussion purposes.

As seen from table 4.5.1, the WCC component contribution shows a difference when considering the CON vs. CRA group. In the CON group, the $CON_{(pre)}$ and $CON_{(post)}$ lymphocytes contribution to the overall WCC remains basically similar (37.21% and 38.51% respectively). In the CRA group, however, the percentage contribution to the total WCC from the lymphocytes decreases to 20.61%. Thus, not only does the CRA group show a higher average white cell count, the composition of the type of white cells also differs. There may be several explanations for this:

- A lower percentage of lymphocytes contributing to the total WCC are associated with, amongst other immune deficiency diseases, HIV. Although the reported CRA group patients that admitted to having HIV or being on treatment are low, this may a false low due to non-reporting (Brass, *et al.,* 2014).
- It may also indicate a higher relative contribution from neutrophils to the observed increased white cell count in the CRA group (i.e. the increase in WCC is more due to an increase in neutrophils than lymphocytes). Neutrophils mostly defend against bacterial or fungal infections. Neutrophils are also though the most common cell type seen in the early stages of acute inflammation.
    - o The higher percentage contribution of neutrophils to the WCC, most likely though, shows the presence of an acute infective state that predisposes patients to cramping
    - o This acute inflammatory state, or at least a part of it, may possibly be due to an inflammatory reaction to increased amount of muscle breakdown / injury. This would then imply:
- If the cramping process is considered to be responsible for the increase in the muscle damage (raised myoglobin / CK) OR that a progressive increase in the amount of muscle damage leads / contributes to cramping – then it could possibly indicate that there was not (on average) an increased WCC prior to the shift in the CGR group. This however is only speculation and a pre-shift / pre-cramp WCC is needed to verify this. A pre-cramp WCC would, however, mean that you would have to do WCC on every mine worker before their shifts in the hope that one will develop cramps.

TABLE 5.1: WHITE CELL COUNT MAKE-UP IN THE CON VS. CRA GROUP

	WCC	NEUTROPHILS	LYMPHOCYTES	LYMPHOCYTE AS PERCENTAGE OF WCC
Control Pre-shift group	6.10	3.02	2.27	37.21 %of WCC
Control Post shift group	6.58	3.31	2.51	38.15 %of WCC
CRA group	9.12	N/A	1.88	20.61 %of WCC

5.3.2.5 *Other findings worth mentioning*

Liver functions

As mentioned above, and as is the case regarding liver enzymes, there does not seem to be any clinical significant changes in liver enzyme concentrations (cf. Tables 4.6.3 - 4.6.6). The Total serum protein and serum albumin was discussed above.

Acclimatisation

Again as an anecdotal observation (author experience), it is worth mentioning that many of the patients that do present with EAMC do so if they have just come back from a period of annual leave. As such acclimatisation or conditioning seems to play a role in the risk profile for developing EAMC. As mentioned in chapter 2, dialysis (Jenkins & Dreher, 1975) would be an extreme example of plasma volume and electrolyte shifts that happens within a short period of time that is associated with muscle cramping. It could thus highlight some factors that may occur more subtly in athletes and labourers especially when not conditioned. Acclimatisation or conditioning plays an important role in giving the body the ability to regulate or buffer muscle damage, fluid balance or shifts and electrolyte changes (Strydom, *et al.*, 1975). Thus the rate of fluid shifts may be of more importance than the actual amount of shifts in the aetiology of EAMC.

5.4 SUMMARY

5.4.1 Identifying an individual at risk of cramping

In section 5.2.6 a "description of a normal" or cramp-free underground mining employee was presented. Keeping the above description of "normal" in mind, a clinical description of a patient that developed cramps will now be presented.

The high risk for a miner will be a miner that shows up to work on a Tuesday or Wednesday for his shift after he had worked an on weekend (cf. 5.3.1.1). The miner will be on his way to perform his duties, which could be either heavy physical labour (drillers, stope team) or work in a prolonged squatting position (drillers, stopers, winch drivers) (cf. 5.3.1.2). The miner might be a little dehydrated or not optimally hydrated prior to the start of his shift due to not taking enough fluids after his shift when he got home the previous day or he may have had a celebration the previous night where he consumed alcohol that left him a bit dehydrated (cf. 5.3.2.1). The miner might also be suffering from an infection: respiratory, urinary etc. that causes a WCC response even before starting his shift.

During the shift, the miner may be called on to perform more strenuous duties than what he or she is accustomed to. This miner may not have acclimatised properly to this particular physical stress or been on holiday for one to two months and tried to return to his pre-holiday level of exertion immediately, causing muscle fatigue and muscle damage. This miner profile described above will have a higher risk for cramping than his college that doesn't fit this profile. "Recognising" a "cramper" (person at higher risk to cramp during a bout of exercise), one can now advise on preventative strategy even if there are no proven ONE solution for preventing cramps.

One should try to avoid greater than five consecutive days of hard physical work. If one was exposed to heavy physical labour, then this should be followed by a less strenuous working day. If the miner is performing his physical labour in a squatted or cramped position, he or she should rest and stretch on regular intervals (even if it means lying down on his or her back to just stretch their limbs). One should avoid alcohol or other dehydrating substances (e.g. excessive coffee) the previous night and hydrate properly with an isotonic fluid after shift. If one has an infection of any sort that might be causing a WCC response, one should not over-exert oneself during the particular shift as the exertion may be perpetuated further by exercise. During the shift, one should consume isotonic fluids to combat thirst and have a proper lunch break for food. Also, a proper acclimatisation period should be observed when joining the company or returning from leave. The miner should be encouraged to participate and engage fully in the acclimatisation protocol.

5.4.2 Closing remarks

There seems to be an unnecessary polarisation between those for and those against the inclusion of electrolyte and dehydration into the aetiology of EAMC. One of the main arguments against the inclusion of these hypotheses (electrolyte and dehydration) is that the proponents basically fail to link how a systemic abnormality may cause a local disruption in homeostasis. This is a sound argument if we consider electrolyte disturbances and dehydration to be the sole cause of cramping. One should rather see this as part of a collective subset of contributing factors that each add to priming the body's muscles for developing cramps. Single or groups of muscles that do then cramp is being triggered to cramp in the "primed" environment by factors like fatigue.

This "priming- and trigger theory" that is proposed is basically the following: Various factors act as priming agents in muscles. They are the collective product of varying percentage contributions of different factors. They together prime the muscle to cramp following a "trigger" ex. muscle contraction in a fatigued muscle. This could primarily indicate a protective mechanism. The point of this hypothesis in essence is to emphasise that each individual will have different percentage contributions from the different factors. All need to be addressed in an individualised manner, a tick-box manner if you will to find out which particular contributory priming factor / factors are at play in the particular patient and address them on merit.

The available massive amount of data that was generated by this study still possess the untapped potential to be manipulated or rather sorted according to specific criteria to investigate the physiology behind numerous other concepts (for lack of a better word). Two possible examples would be to sort the data using the following as the main selective sorting criteria:

1. Sorted according to days of the week. This would shed more light on the sequential compensatory physiological adaptations to changes or accumulations of for example CK levels; and
2. Sorted according to myoglobin levels. If one were to consider the severity of the cramping as a relationship to the myoglobin level i.e. muscle damage was considered, in main, to be as a result of cramping (muscle spasm), one could deduce certain accompanying physiological changes in biochemical factors related to this severity of muscle damage or cramping if you will.

This research will hopefully lay a foundation for future research, to determine the association of identified factors with EAMC.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 OPENING REMARKS

Chapter 6 will be dedicated to suggestions when performing similar studies in similar populations. The lessons learnt include lessons on the study design, study participants and study environment. The author will now present his own limitations and the limitations of this particular study with suggestions for future studies.

6.2 STUDY DESIGN

6.2.1 Attracting mining employees to participate

6.2.1.1 *Incentives*

In South Africa, the mining sector relies heavily on incentives to boost production efforts. Every aspect of mining, production, health and safety, campaign participation etc. relies on incentives to motivate employee cooperation. Proper funding thus needs to accompany any future research as it is a good motivator and borderline necessity in this particular population to ensure decent sample sizes.

6.2.1.2 *Cultural considerations*

This population also holds strong cultural and superstitious beliefs. This was evident in the situation regarding the disposal of the blood after testing. Several potential participants (unbeknownst to the author) did not want to participate due their objections about what we did with their blood after testing.

6.2.2 Choosing participants for the CON group

One should aim for a more structured participant make-up in the formulation of the CON group. The aim should be the sampling of CON group participants to cover the most likely occupations for the development of cramping (as described in this study: drillers, stope team members, and winch operators). Furthermore, these high risk occupation participants should have representation on all the days of the week. This is to compare to the CRA (that cannot be predicted) that presented on a specific day (for example on a Tuesday).

6.2.3 Location for study

The study should be performed in one shaft to be able to ensure proper training of staff and employees and to be able to ensure quality control as far as possible in order to reduce (even if to a minor degree) the multitude of possible variables that might influence the interpretation of the results.

6.3 FOLLOW-UP STUDY DESIGNS

6.3.1 Temperatures

6.3.1.1 *Environmental temperatures*

The addition of the prevailing environmental conditions (temperatures and humidity) on the specific level in the shaft where the participants work, especially in the CRA of participants, on the incident day (day that cramping occurred) or in the CON group on the test day would have been of great value. This information on environmental conditions are collected on a daily basis by the environmental officers and stored in their archives. The sheer size and the fact that the information (gathered over one and a half years) on the CRA was collected retrospectively and from multiple different shafts spread over a wide area made it almost impossible for the author to collect by himself. Thus, again a well-funded research project could possibly afford at least two assistants to gather this information.

6.3.1.2 *Body temperatures*

The acceptance of the temperatures in the CRA was problematic as the method could not be verified or controlled due to the fact that the incidents took place again over a wide range of shafts with their own staff. It could also not be verified whether the temperatures were taken rectally and whether it was taken before or after they cooled the patient down with water and air-jets as described in Chapter 2. The suggestion is to try to ensure that rectal temperatures are taken at the onset of EAMC prior to cooling down the patient by using the correct technique. The correct technique should be taught to all employees at shafts or at least to the safety officers on the team. They should also use rectal thermometers that is not made of glass (if available) to avoid further injury in the restless patient.

6.3.2 Blood sample taking

6.3.2.1 *Taking of samples*

Where possible, blood samples should be taken without a tourniquet. Prolonged tourniquet time will influence, for example, serum albumin and serum calcium.

6.3.2.2 *Transportation of samples*

Blood samples should be transported to the laboratory for testing immediately using the proper cold-chain method if indicated. Alternatively and preferably, the samples should be tested immediately on site with portable, properly calibrated haematology and biochemistry machines. This is to avoid haemolysation of the blood samples.

6.3.3 Hydration

6.3.3.1 *Correction for dehydration of fluid volume loss*

Haemoconcentration or even dilution on the other end of the spectrum leads to misleading results related to especially serum electrolyte concentrations. To compensate for this, the study needs to have follow-up investigations in order to more accurately interpret and comment on the incident date (day zero or day of EAMC) findings. Either of the two described methods, serum total protein (Ohira *et al.*, 1977) or Hb / Hct (Dill and Costill 1974) could be used to calculate or compensate for haemoconcentration. This would mean that blood has to be taken on the incident day (day 0), day 1, 2 and 7 post incident and this will again have financial implication.

6.3.3.2 *Specific factors*

Creatinine & GFR

Due to the presence of increased muscle damage that accompanies heavy manual labour in this particular group of participants one should also include a urine creatinine as to better understand the stresses on the kidney functions. For the same reason, the disputed method of calculating GFR i.e. the MDRD method should preferably not be used.

Alcohol use

Anecdotally (and this is a well-known fact amongst the employees) the chances of cramping increase significantly if they had a heavy night of alcohol consumption the previous evening. The possible use of either an alcohol breathalyser or the new fingerprint alcohol test should exclude participants from entering the shaft and becoming part of the study due to the development of cramping.

6.3.4 Inflammation / Infection

In order to minimise the chances of patients entering the shaft with an increased WCC as a result of either a respiratory or urinary or any other source of infection one could advocate the use of urinary dipsticks post-incident to exclude a urinary tract infection which is common in this population. One could also use an infrared scanner or temperature measurement prior to entering the shaft to minimise the chances of employees entering the shaft and again becoming part of the study as a participant with cramping.

6.4 FINAL THOUGHTS

The author acknowledges the limitations of the current study as mentioned throughout this study. As a first-time researcher and author many valuable lessons was learnt - not only on the topic of EAMC - but on the topic of study design and approaches to the performance of studies in this challenging population and environment. This experience will be invaluable in future similar and follow-up and new studies.

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APPENDIX A

WORK PLACE INFORMATION FOR SUSPECTED HEAT ILLNESS CASES

APPENDIX A

WORK PLACE INFORMATION FOR SUSPECTED HEAT ILLNESS CASES

(Completed at work place)

Name:	Mine:	Shaft:
Patient number:	Section:	Gang:

Date and time of shift	…./…./…. ….h….
Time of heat symptoms	….h….
Worker temperature	Rectal ……………………….. Oral……………………………..
Employee conscious/awake	Yes………………………….. No……………………………….
Dizziness	Yes ……………………………. No……………………………….
Vomiting / nausea	Yes ……………………………. No……………………………….
Aggressive	Yes ……………………………. No……………………………….
Pulse rate	Very fast Fast Slow
Breathing	Very fast Fast Slow
Muscle cramps in more than one place	Yes ……………………………. No……………………………….
Other	

Distance from drinking water	Estimated …….. meters
Estimated liters of fluid taken by employee	
Environmental shift information	Wet bulb temperature………………. Dry bulb temperature………………. Air velocity………………………………… Measure date……./……/……

What work was the employee doing?	
Was the employee well at the beginning of the shift?	
Was the area hotter than usual?	
Was there an airflow problem?	
Was the employee the only one complaining of heat illness? If not, provide details.	
Was the employee doing any heavier work than is normally expected? If so, please state.	
Did the employee have…?	Alcohol day before Y/N Breakfast Y/N
Any other information	

NAME: …………………………………………. SIGNATURE: …………………………………………….

APPENDIX B

QUESTIONNAIRE COMPLETED ON ARRIVAL IN THE EMERGENCY DEPARTMENT

APPENDIX B

QUESTIONNAIRE COMPLETED ON ARRIVAL IN THE EMERGENCY DEPARTMENT

Name: .... **Patient number:** ....
Date: ....
Rectal temperature in casualties: ....
Bloods taken: LFT, U&E, FBC, GLUCOSE, MYOGLOBIN, CK

HISTORY

Working level		
Temperature at work place		
Previous/chronic illness		
Chronic medication		
Time of onset of symptoms		
Previous heat related illness		
Alcohol use in the last 48 hours		
Fluid intake during shift		
Nature of work employee was doing		

SYMPTOMS

Cramps Y/N	Nausea Y/N	Vomiting Y/N
Dizziness Y/N	Abdominal pain Y/N	Headache Y/N
Fainting Y/N	Confusion Y/N	Aggression Y/N
Other		

NURSE ON DUTY: .... **SIGNATURE:** ....
DATE:...

RESULTS

WCC.......................	CREATININE..................	SODIUM.......................	CK.................................
UREA......................	GLUCOSE......................	MYOGLOBIN................	OTHER:.........................

DIAGNOSIS: ....

DOCTOR ON DUTY:........................... **SIGNATURE:** .... **DATE:** ....

APPENDIX C

MEDICAL INFORMATION REGARDING CONTROL GROUP VOLUNTEERS

APPENDIX C

MEDICAL INFORMATION REGARDING CONTROL GROUP VOLUNTEERS
(FOR PRE-SHIFT AND POST-SHIFT USE)

Patent company number (for control purposes only) ____________

1 Study Participant number: ____________ 1-3

2 Date: ____________ 4-7

3 Day of the week: ____________ 8

4 Time shift Ends: ____________ 9-12

5 Environmental conditions at work area

5.1 Wet bulb temperature (degrees Celcius) ____________ 13-15

5.2 Dry bulb temperature (degrees Celcius) ____________ 16-18

5.3 Humidity ____________ 19-20

5.4 Air speed ____________ 21-22

6 Biometrics

6.1 Worker weight (kg) ____________ 23-25

6.2 Worker height (cm) ____________ 26-28

6.3 BMI ____________ 29-30

6.4 Hip circumference (cm) ____________ 31-33

6.5 Waist circumference (cm) ____________ 34-36

6.6 Hip to Waist Ratio ____________ 37-39

6.7 Abdominal circumference (cm) ____________ 40-42

7 Vital signs

7.1 Blood pressure ____________ 43-48

7.2 Pulse rate ____________ 49-51

7.3 Temperature (1decimal)

Rectal	____________	52-54
Axillary	____________	55-57

8 Urine Dipstix

8.1	Leucocytes	Neg	Tr	1+	2+	3+			58
8.2	Nitrates	Neg	Pos						59
8.3	Protein	Neg	Tr	1+	2+	3+	4+		60
8.4	pH								61
8.5	Blood	Neg	Tr	1+	2+	3+			62
8.6	SG	1.000	1.005	1.010	1.015	1.020	1.025	1.030	63
8.7	Ketones	Neg	Tr	1+	2+	3+	4+		64
8.8	Glucose	Neg	Tr	1+	2+	3+	4+		65
9	Episode of Cramping during shift	Yes	No						66
9.1	Extent of cramping	Localized	Generalised – abdominal included						67

10	**Health question following shift**			68
10.1	**History of vomiting/ nausea/ diarrhoea during shift**	**Yes**	**No**	69
10.2	**Dizziness?**	**Yes**	**No**	70
10.3	**Muscle stiffness?**	**Yes**	**No**	71

11 Fluid Intake during shift

11.1 Distance from drinking water **Estimate in meters: ______________ m** 72-74

11.2 Litres of fluid taken by employee during shift: ______________ L 75

11.3 Type of fluid? ______________________________ 76

12	**Was the employee doing his normal duties?**	**Yes**	**No**		77
13	**Did the employee perceive his / her work as:**	**Normal**	**More strenuous**	**Less strenuous**	78
14	**Was the area perceived as hotter than usual?**	**Yes**	**No**		79
15	**Was there an airflow problem?**	**Yes**	**No**		80

16	**Bloods taken before the shift**			
16.1	**FBC**	**Yes**	**No**	81
16.2	**U&E + Cr**	**Yes**	**No**	82
16.3	**LFT**	**Yes**	**No**	83
16.4	**Glucose (random)**	**Yes**	**No**	84
16.5	**CMP**	**Yes**	**No**	85
16.6	**Myoglobin**	**Yes**	**No**	86
16.7	**CK**	**Yes**	**No**	87

PATIENT: NAME: ....
SIGNATURE: ....
DOCTOR: NAME: ....
SIGNATURE: ....

Blood results – Control sheet

Full Blood Count (FBC)		
Red cell count (4.5-5.9 x 10^12/l)		1-2
Haemoglobin (13-18g/dL)		3-4
Haematocrit (0.4-0.5L/L)		5-6
MCV (81-100fl)		7-9
MCH (28-35pg)		10-12
RDW (10-15)		13-14
WCC (4-11 x 10^9/l)		15-16
Neutrophils (2-7.5 x 10^9/l)		17-18
Lymphocytes (1-4 x 10^9/l)		19-20
Monocytes (0-0.95 x 10^9/l)		21-23
Eosinophils (0-0.4 x 10^9/l)		24-25
Neutrophil bands (0-0.7 x 10^9/l)		26-27
Platelet count (140-420 x 10^9/l)		28-30

Kidney function (U&E + Cr)

s-Sodium (136-144 mmol/L)		31-33
s-Potassium (3.5-5.1mmol/L)		34-35
s-Chloride (98-110mmol/L)		36-38
s-CO_2 (22-30mmol/L)		39-40

s-Anion Gap (5-15mmol/L)					41-42
s-Urea (2.5-6.7mmol/L)					43-44
s-Creatinine (57-113umol/L)					45-47
MDRD (GFR estimate) (>90mL/min)					48-49

Glucose				50-51

Cardiac markers

Blood Myoglobin (16-76ng/mL)					52-54
s-Total CK (15-195u/l 37ºC)					55-58
CK-MB Mass (0.6-6.3ng/mL)					59-60

Liver Functions

s-Total Protein (60-82g/L)					61-63
s-Albumin (37-52g/L)					64-65
s-Globulin (18-36g/dL)					66-67
s-Albumin/Globulin Ratio (0.9-2.7)					68-69
s-Total Bilirubin (2-20umol/L)					70-71
s-Conjugated Bilirubin (0-8umol/L)					72-73
s-Unconjugated Bilirubin (2-14umol/L)					74-75
s-Alkaline Phosphatase (40-120u/L 37ºC)					76-78
s-Gamma GT (5-50u/L 37ºC)					79-81
s-ALT (10-40u/L 37ºC)					82-84
s-AST (10-40u/L 37ºC)					85-87

Calcium

Tot. Calcium (2.1-2.6 mmol/L)				88-89
Cor. Calcium (2.1-2.6 mmol/L)				90-91

Magnesium (0.70-1.05 mmol/L)					92-94

Phosphate (0.80-1.40 mmol/L)					95-97

APPENDIX D

CONSENT TO PARTICIPATE IN RESEARCH

APPENDIX D

CONSENT TO PARTICIPATE IN RESEARCH

PROJECT TITLE: PREVALENCE AND BLOOD PROFILE ANALYSIS OF SOUTH AFRICAN GOLD-MINERS WORKING UNDERGROUND WHO PRESENT WITH EXERCISE-ASSOCIATED MUSCLE CRAMPS AT WORK

You have been asked to participate in a research study.

You have been informed about the study by Dr. Rudolph De Wet

You have been informed about any available compensation or medical treatment if injury occurs as a result of study-related procedures;

You may contact Dr. Rudolph De Wet at (057) 916 7289 / 084 580 6734 any time if you have questions about the research or if you are injured as a result of the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

________________________ ____________________

Signature of Participant Date

________________________ ____________________

Signature of Witness Date

________________________ ____________________

Signature of Translator Date

INFORMATION DOCUMENT

PROJECT TITLE: PREVALENCE AND BLOOD PROFILE ANALYSIS OF SOUTH AFRICAN GOLD-MINERS WORKING UNDERGROUND WHO PRESENT WITH EXERCISE-ASSOCIATED MUSCLE CRAMPS AT WORK

Dear Participant

Introduction:

I, Dr. Rudolph De Wet from the department Sports & Exercise medicine at UOFS and employed by Harmony gold mine am doing research on body cramps in the gold mining sector. Research is just the process to learn the answer to a question. Up till now there has not been data available regarding physical parameters and blood results related to mine workers working underground. We believe that collecting this data will help us to better understand the environmental and physiological stresses faced by workers so we can be able to devise proper preventative and management strategies

Invitation to participate: We are asking/inviting you to participate in this research study*.*

What is involved in the study –

- Procedure: For collecting all of the information:
    - On the day that the tests will be performed:
        - Patients will present prior to their shift at 06h00
        - Basic data will be recorded on a pre-devised form
        - Baseline bloods will now be taken
        - The patients will then go underground for their shift
        - On completion of their shift the participants will present immediately at the medical station where the blood will be drawn again and some of the data collection repeated
    - For blood taking:
        - You will be asked to provide a sample of blood +/- 15ml (the body has +/- 5L of blood). The blood will be taken with a needle and from your arm. The blood will then be sent to the laboratory for tests. After the tests the bloods will be destroyed according to standard procedures.
- Time involvement: Your participation in this experiment will take approximately:
    - Pretest and consent form counseling session 30min
    - On the day examination and baseline blood tests 30min
    - After-shift blood drawing and examination 30min

Risks of being involved in the study: The risks associated with this study are slight discomfort or bruising from the blood drawing. If there is any incidental abnormality found in your blood results, you will be investigated further and managed according to normal medical standards and protocols.

Benefits of being in the study. There is also the added incentive that you will be helping, in the creation of an underground mineworker profile that will hold benefit for you and all mine workers' health management in the future.
You will not be paid to participate in this study. There will however be an incentive for those who do volunteer and complete the study.

Alternative procedures or courses of treatment that might benefit the subject. If there is any incidental abnormality found in your blood results, you will be investigated further and managed according to normal medical standards and protocols.

The subject will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council.

If results are published, this may lead to individual/cohort identification.

Contact details of researcher(s) – for further information/reporting of study-related adverse events.

- Dr. Rudolph De Wet -057 916 7289 (work)
  -084 580 6734 (mobile)
- Ethics Committee UOFS

Contact details of REC Secretariat and Chair – for reporting of complaints/problems.

APPENDIX E

CONSENT TO PARTICIPATE IN RESEARCH - SOTHO

APPENDIX E

CONSENT TO PARTICIPATE IN RESEARCH - SOTHO

Tumello ya ho sebediswa dipatlisisong.

Sehloho sa qalo tshebeto: Tlhokomediso ya ho ata le patlisiso ka madi ya basebetsi ba merafong ya gauta Afrika Borwa ba bonahalang le ho hlahella ka dikerempe tsa mesifa ka baka la mosebetsi. O kopilwe ho emela dipatlisiso.

O qaqiseditswe ka ha dipatlisiso ke Ngaka Rudolph De Wet.
O fumantshitwe lesedi ka tefo kapa ditlhare mabapi le ha o ka hlahelwa ke diphetoho tsa bophelo dipatlisisong.
O ka letsetsa Ngaka Rudolph De Wet ho 051 916 7288/084 580 6734 nako efe kapa efe ho fumantshwa tlhakisetso ka ha dipatlisiso kapa temalo e ka bakwang ke sepheto sa dipatlisiso.
O ka fumana lesedi ho Mongodi wa Lefapha la Thibelo ya Boatla Lefapheng la tsa Bophelo la Diphuputso Univesiting ya UFS mohaleng (057)4052812 ha o na le dipotso ka tokelo ya hao ya ho fuputswa.
Ho nka karolo ha hao ke boithaopo mme o dumelletswe ho ka ikhula neng kapa neng ntle le ho hlekefetswa kapa ho nkelwa seo o se tshepisitsweng kapa ho hlekefetswa ha o nka sepheto sa ho se hlole o nka karolo.
Ha o dumela ho nka karolo o tla fumanatshwa leqephe le tekennweng le le qopiditsweng hantle le hlahiso leseding ya dipatlisiso e khutsufaditsweng.
Dipatlisiso tsohle , ho kenyeletsa se ka hodimo ke se hlaloseditswe ka molomo. Ke a utlwisisa ho nka karolo ha ka dipatlisisong le ho dumela ho nka karolo ke boithaopo.

Tekena Mofuputswi Letsatsi

Tekena Paki Letsatsi

Tekena Mohlalosetsi Letsatsi

TLHAHISO LESEDING

Sehloho sa thuto: Tlhokomediso ya ho ata le patlisiso ka madi ya basebetsi ba merafong ya gauta Afrika Borwa ba bonahalang le ho hlahella ka dikerempe tsa mesifa ka baka la mosebetsi.
Monka karolo ya ratehang .
Lehlaso:
Nna ngaka Rudolph De Wet ho tswa ho ba Lefapha la tsa Boikwetliso le Dipapadi la tsa Meriana wa UOFS ke le mosebetsi morafong wa Harmone ya etsang dipatlisiso ho fuputsa dikerempe merafong ya gauta.Phuputso empa ele ketsahalo ho ithuta ho araba potso e itseng. Ho fihlela ha jwale ha ho so hobe le se ngotsweng ho fumana ketso kakaretso le sephetho sa madi se tobaneng le basebetsi ba merafong ba sebetsang tlase mpeng ya lefatshe. Re dumela hore ho batlisisa ka hohle ho tla thusa ho bebofatsa kutlwisiso ya sebaka le khatello ya maikutlo ya tshebetso e tobileng basebetsi ho ka fumana leano la ho thusa.
Memo ya ho nka karolo : Re le memela ho nka karolo ya dipatlisiso thutong ena.
Ke eng se batlahalang thutong ena –
Tshebetso : Ho fumana tsebo yohle**.**
Mohla tsatsi la tlhatlhobo.
Basebetsi batla iponahatsa pele ho tshebetso ka 06h00.
Dipatlisiso di tla ngolwa leqhepeng la dipatlisiso.
Mosebetsi a nto ya mosebetsing mpeng ya lefatshe .
Ka mora tshebetso mosebetsi a iponahatse hang hang sepetleleng sa shafong moo
Madi a tla hulwang hape mme hlahlobo e phetwe.
Ho hule madi:
O tla koptjwa ho hulwa bonyane 15ml ,banyane mmele o na le litara tse 5 tsa madi .
RE tla sebedisa nale ho hlabo mothapo ho hula madi. Madi a tla romelwa
Laboratoriamong ho hlahlobjwa, mme a fuputswe a nto lahlwa ka mokhwa o tshwanelehileng.
Nako ya diteko: Hona ho tla o tshwarella bonyane:
Tlhalosetso le ho tekenela tumellano metsotso e 30
Ka tsatsi la hlahlobo le ho hula madi metsotso e 30

Ho hula le ho hlahloba madi ka mora mosebetsi metsotso e 30
Ditla morao tsa ho ba mofuputswi thutong :Ditla morao di batla di se monatenyana.Baka seo madi a hutsweng ho sona se ka talafala .Ha sepheto se sa kgotsofatsa ho ka tshwanela ho phetwe ho nka madi ho sebediswa metjha e molaong.
Molemo wa hoba mofuputswi thutong: Ka hodimo o tla be o thusitse basebetsi mmoho bohle ba sebetsang mpeng ya lefatshe merafong le Lefapha la tsa Bophelo molemong le bokamosong ba hao le bohle.
Ha ho moputso ho nkeng karolo thutong.Empa ho tla ba le moropotso ho baithaopi ba fihleletseng sepheto.
Se ka etswang kapa kalafo e ka bang molemong wa ba nka karolo.Ha ho ka ha fumaneha phoso sephetong sa madi ,o tla fuputswa ho ya pele mme o thusahale ka molao wa kalafo o tshwanelehileng molaong.
Monka karolo o tla fumantshwa hlahiso leseding nakong ya diphuputso le ka sepheto sa diphuputso.
Ho nka karolo ke boithaopo, mme khanetso ho nka karolo e ka se be kgatello kapa ho lahlehelwa ke melemo e o tshwanetseng;monka karolo a ka ikhula nako efe kapa efe ntle le kotlo kapa tahlehelo ya seo tshwanetseng.
Lekunutu tshireletso: Ho tla etswa ka hohle ho tshireletsa botho empa e ka se be ka hohle hohle sephetho se tla patlalatswa ka molao wa tshireletso.
Ba diphuputso ba dumelletsweng ba ka fumantshwa ho shebisisa le ho batlisisa jwalo ka ba Lefapha la Tshireletso ya tsa Botho le Meriana Dipatlisisong le ba Tshireletso yaTshebediso ya tsa Bongaka.
Phetho ha se phatlalatswa hona ho ka lebisa phatlalatsong ya mofuputswi ya hlwailweng.
Phumaneho ya Bofuputsi- mabapi le phumaneho ya diphatlalatso tsohle le ditletlebo.

Ngaka Rudolph De Wet - 057 916 7289(Mosebetsing)
- 084 580 6734 (Mohala wa nako tsohle)

Lefapa la thibelo ya Boatla UFS
Tsa Mongodi wa REC le Modula Setulo –ho ntsha ditletlebo le bothata.

APPENDIX F

SHAPIRO WILK DATA DISTRIBUTION TEST RESULTS

APPENDIX F

SHAPIRO WILK DATA DISTRIBUTION TEST RESULTS

VARIABLE	P-VALUE
Con_Alb_post	0.977
Con_Alb_pre	0.780
Con_AlkPhos_post	0.843
Con_AlkPhos_pre	0.934
Con_ALT_post	0.000
Con_ALT_pre	0.000
Con_Arm_post	0.018
Con_Arm_pre	0.199
Con_AST_post	0.069
Con_AST_pre	0.021
Con_Ca_post	0.331
Con_Ca_pre	0.421
Con_Calf_post	0.382
Con_Calf_pre	0.135
Con_cCa_post	0.134
Con_cCa_pre	0.625
Con_CK_post	0.003
Con_CK_pre	0.003
Con_CL_post	0.688
Con_CL_pre	0.892
Con_CO2_post	0.624
Con_CO2_pre	0.686
Con_Crea_post	0.345
Con_Crea_pre	0.634
Con_DBP_post	0.934
Con_DBP_pre	0.780
Con_GGT_post	0.008
Con_GGT_pre	0.002
Con_Gluc_post	0.522
Con_Gluc_pre	0.358
Con_Hb_post	0.247
Con_Hb_pre	0.035
Con_Hct_post	0.771
Con_Hct_pre	0.140
Con_Height_post	0.889
Con_Height_pre	0.889
Con_Hip_post	0.408
Con_Hip_pre	0.327
Con_HR_post	0.735
Con_HR_pre	0.148
Con_K_post	0.567
Con_K_pre	0.856
Con_Lymph_post	0.284
Con_Lymph_pre	0.411
Con_Mass_post	0.108
Con_Mass_pre	0.117
Con_MDRD_post	0.001
Con_MDRD_pre	0.000
Con_Mg_post	0.990
Con_Mg_pre	0.361
Con_Myo_post	0.002
Con_Myo_pre	0.302

Con_Na_post	0.536
Con_Na_pre	0.262
Con_Osmo_post	0.357
Con_Osmo_pre	0.094
Con_Phos_post	0.485
Con_Phos_pre	0.554
Con_Prot_post	0.254
Con_Prot_pre	0.003
Con_SBP_post	0.840
Con_SBP_pre	0.219
Con_Temp_post	0.930
Con_Temp_pre	0.031
Con_Urea_post	0.662
Con_Urea_pre	0.081
Con_Waist_post	0.786
Con_Waist_pre	0.874
Con_WCC_post	0.014
Con_WCC_pre	0.019
Cra_Alb_post	0.901
Cra_AlkPhos_post	0.021
Cra_ALT_post	0.437
Cra_AST_post	0.307
Cra_CK_post	0.227
Cra_Cl_post	0.256
Cra_CO2_post	0.117
Cra_Crea_post	0.638
Cra_GGT_post	0.001
Cra_Gluc_post	0.163
Cra_Hb_post	0.463
Cra_Hct_post	0.845
Cra_K_post	0.881
Cra_Lymph_post	0.980
Cra_MDRD_post	0.000
Cra_Myo_post	0.019
Cra_Na_post	0.103
Cra_Osmo_post	0.541
Cra_Prot_post	0.369
Cra_Temp_post	0.032
Cra_Urea_post	0.217
Cra_WCC_post	0.489

APPENDIX G

ETHICAL CLEARANCE

APPENDIX G

ETHICAL CLEARANCE

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS UV

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Ms H Strauss/jdpls

2014-01-27

REC Reference nr 230408-011
IRB nr 00006240

DR R DE WET
DIVISION OF SPORT AND EXERCISE MEDICINE
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr De Wet

ECUFS NR 198/2011
PROJECT TITLE: PREVALENCE AND BLOOD PROFILE ANALYSIS OF SOUTH AFRICAN GOLD-MINERS WORKING UNDERGROUND WHO PRESENT WITH EXERCISE-ASSOCIATED MUSCLE CRAMPS AT WORK

- You are hereby kindly informed that the Ethics Committee approved the following at the meeting held on 21 January 2014:

- ***Project title changed to: "Prevalence and blood profile analysis of South African Gold Miners working underground who present with exercise-associated muscle cramps at work"***

- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.

- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

- The Committee must be informed of any serious adverse event and/or termination of the study.

- All relevant documents e.g. signed permission letters from the authorities, institutions; changes to the protocol, questionnaires etc. have to be submitted to the Ethics Committee before the study may be conducted (if applicable).

- A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

- Kindly refer to the ETOVS/ECUFS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

....

DR SM LE GRANGE
ACTING CHAIR: ETHICS COMMITTEE

Cc Ms S Van Der Merwe