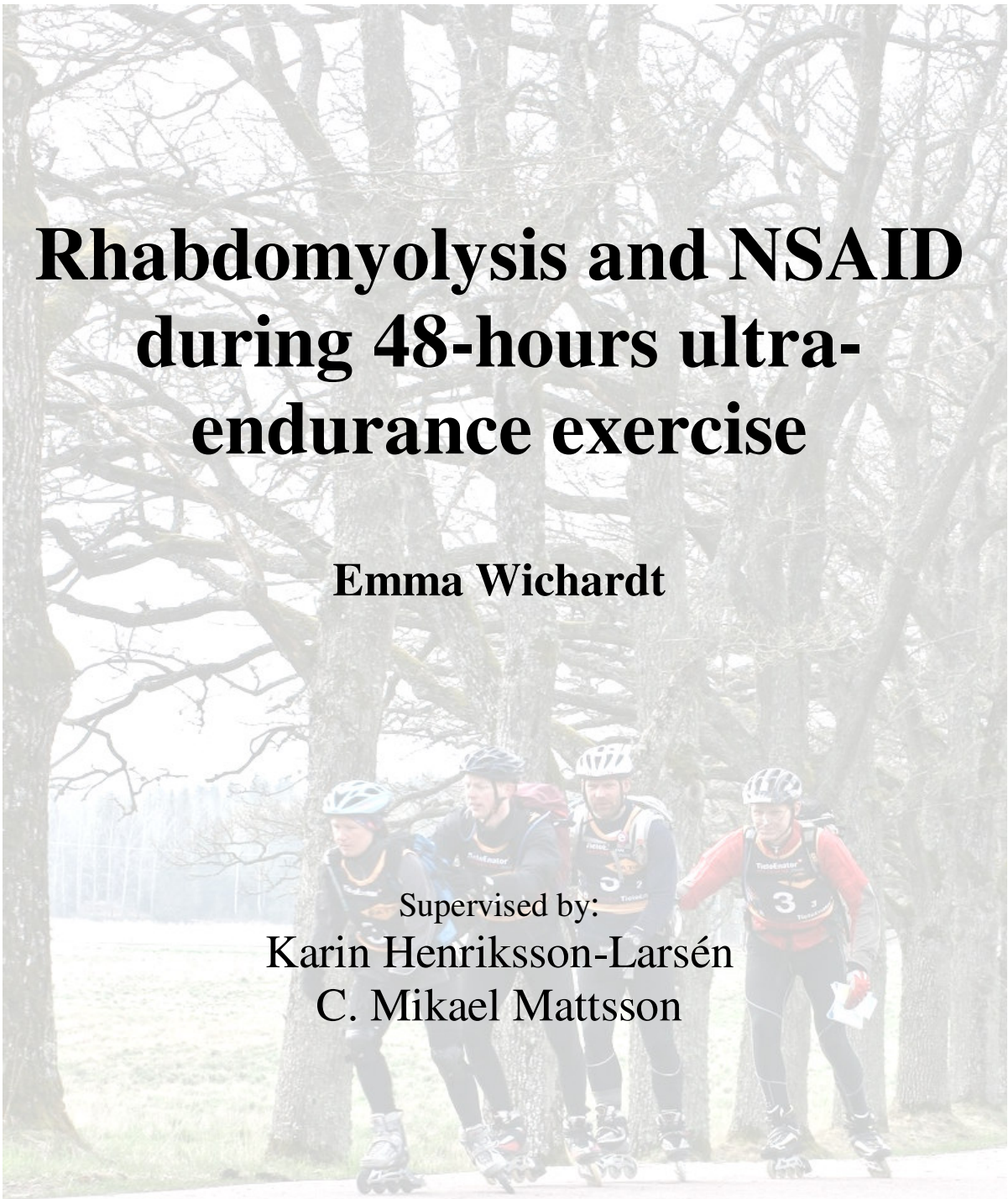
Rhabdomyolysis and NSAID during 48-hours ultra-endurance exercise

Emma Wichardt



Supervised by:
Karin Henriksson-Larsén
C. Mikael Mattsson

Emma Wichardt
Sports medicine department
Surgery and perioperativ science
Umeå University
901 87 Umeå
Phone +46 90 785 48 13 Fax +46 90 13 56 92
E-mail : emawit04@student.umu.se

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Abstract

Purpose: This study examines if rhabdomyolysis with myoglobinemia exists during a 48+ hour ultra-endurance adventure race, if there is a relationship with intake of NSAID, and how this affects race time as well as perceived pain, exertion and performance. **Method:** Blood samples for myoglobin analyses were taken from 20 subjects before the start, half-way through, and within 30 minutes of the finish line. The subjects filled out a survey asking if they had taken any NSAID within 12 hours of blood sampling. They also stated their level of exertion and pain before the sampling (rated with the Borg-RPE scale and the Borg-CR scale), as well as their perceived performance. **Results:** There was a significant raise in overall myoglobin halfway through the race and after the race compared with before the start of the race, ($p<0.001$). There was also a significant difference ($p<0.05$) between the two groups, with the NSAID group having lower myoglobin levels than the non-NSAID group. The results also show that higher levels of myoglobin before and during the race are correlated to better race results ($r=-0.512$; $p=0.026$), lower perceived pain ($r=-0.455$; $p=0.44$) and exertion ($r=-0.673$; $p=0.003$) and higher perceived performance ($r=-0.472$; $p=0.038$). **Conclusion:** This study both confirms and contradicts some earlier studies, with a lesser degree of rhabdomyolysis after NSAID intake. But the really interesting result is that myoglobin levels seem to have a positive effect on race results as well as the athletes' perceptions of level of pain, exertion, and performance.

Keywords

Adventure racing, multisport, NSAID, myoglobin, myoglobinemia.

Introduction

Strenuous exercise in all forms can result in rhabdomyolysis, which is a severe and acute skeletal muscle damage resulting in sarcolemma disruption. This leads to a release of intracellular muscle proteins into the plasma. Complications may be electrolyte abnormalities, compartment syndrome, and acute renal failure. The clinical picture of rhabdomyolysis may include muscle soreness, reduction of the range of motion, decreased muscle strength, black urine and, in severe cases, acute renal failure (Heled et al. 2005).

Acute renal failure is the most serious and the most feared complication of rhabdomyolysis. But there is a lower incidence of acute renal failure in patients with exercise-induced rhabdomyolysis (exertional rhabdomyolysis) compared with patients with non-exercise-induced rhabdomyolysis (Sinert et al. 1994). The most common causes of non-exercise-induced rhabdomyolysis are trauma and alcohol intake, but may also include drug use, for example statins (Evans et al. 2002; Thompson et al. 2003).

One of the intracellular muscle proteins released into the plasma as a consequence of rhabdomyolysis is myoglobin (Mb), which causes subsequent myoglobinemia and myoglobinuria. Bagley et al. (2007) stated that S-Mb levels can rise within hours of muscle damage, but that it can also return to normal within one to six hours if continuous muscle injury is not present.

Rhabdomyolysis, especially exertional rhabdomyolysis, is likely under-reported (Brown et al., 2004; Sauret et al., 2002). However, exertional rhabdomyolysis is generally resolved without consequences (Clarkson, 2007). It does not become clinically relevant until the muscle proteins released into the circulation causes acute renal failure. Laboratory studies of exertional rhabdomyolysis after eccentric exercise have recently shown that creatin kinase (CK) and Mb levels can increase significantly, with CK levels up to 80 000 U/L without causing renal failure (Clarkson et al., 2006). It supports the hypothesis that marked CK and Mb elevations in response to exercise in healthy individuals are not sufficient to induce renal compromise. Other factors, such as dehydration and heat stroke, must be present to cause clinically relevant exertional rhabdomyolysis, as suggested by Clarkson et al. (2006) as well as Clarkson & Eichner (2006).

Adventure racing (AR)

Adventure racing is a combination of three or more extreme/outdoor sports that includes, at a minimum, running, mountain biking and paddling. Other disciplines vary with the location of the race and the time of year but it can include cross-country skiing, mountaineering, climbing, in-line skating, snow shoeing, and river rafting. During these competitions participants have to navigate, through a number of check-points, from start to finish. A race can be from 4 hours up to 7 days, covering up to 800+ kilometers. The races are non-stop and the teams are often self-supported with food and water for up to 24 hours. There is little or no sleep or rest during a race. It is up to each team to decide if they are going to stop and sleep, while the race clock keeps going. A team consists of four individuals, at least one of each gender, but the typical team is made up of three men and one woman.

AR puts extreme physical and psychological demands on the participants due to its extreme duration and non-stop nature. The teams compete through a variety of weather and harsh environments where the team's speed is dictated by its weakest team member. There are frequently small injuries and blisters along the way, with participants pushing through comfort levels. It is hard to eat and drink enough and over the course of a typical race competitors are unable to consume enough calories to offset their energy use (Zimberg et al. 2008).

AR is a relatively new sport and the research about it is still sparse. Studies have been performed on the epidemiology of injuries in AR athletes. Fordham et al. (2004) studied the impact of the demographics and training characteristics of AR athletes on injury location and characteristics. Several studies have been race-specific: the Southern Traverse 2003 in New Zeeland, Primal Quest 2002 and Primal Quest 2003, both in the US, have been studied in relation to injury characteristics (Townes et al. 2004; McLaughlin 2006; Anglem et al. 2008; Lucas et al. 2008) The nutritional intake during racing and training is an other area that has been shown interest (Zalcman et al. 2007; Zimberg et al. 2008). One study has examined how the heart is affected during AR (Ashley et al. 2006).

The prevalence of altitude illness, including both the factors contributing to its development and the resulting withdrawal from competition, during an "expedition length adventure race" (i.e. 4 or more non-stop racing days) has been studied by Talbot et al. (2004). Several outbreaks of infectious diseases have been reported and studied, for example an outbreak of leptospirosis in Eco-Challenge in Malaysia 2000 (Sejvar et al. 2003) and 13 cases of African tick-bite fever, caused by Rickettsia africae, in competitors after an adventure race in South Africa (Fournier et al. 1998).

Musculoskeletal injury and complaint is very commonly reported during and after an adventure race. 38 out of 48 racers (79%) at the Southern Traverse 2003 had musculoskeletal injuries after the race (Anglem et al. 2008). All of the racers (100%) experienced pain during or after the race. It is therefore reasonable to believe that there is a certain degree of rhabdomyolysis during an ultra-endurance event like AR, but no previous research on the topic has been conducted.

Ultra-endurance exercise and rhabdomyolysis

There are many studies of rhabdomyolysis during marathon races, and also a few during ultra-distance running, as well as reports of exertional rhabdomyolysis leading to renal failure after military marches and body building (Uberoi et al. 1991; Arányi & Radó 1992).

During a 246 km continuous running race, Skenderi et al. (2006) found the highest levels ever reported of muscle and liver damage indicators, as a result of prolonged exercise. No severe symptoms that required hospitalization were observed in any of the racers. This suggests that asymptomatic exertional rhabdomyolysis can be caused even by moderate-intensity exercise of prolonged duration.

Fallon et al. (1999) investigated biochemical changes related to muscle breakdown and hepatic damage in the serum of participants in a 1600 km ultra-marathon run. Their conclusion was that a wide range of biochemical perturbations occur during ultra-marathon running but a number of variables remain within normal limits despite severe physical stress.

The time course of increases in enzymatic indicators of muscle damage indicated that duration of running was not the sole determinant of such increases.

Measurements on twenty-five participants in a triathlon competition showed that a significant correlation existed between average S-Mb and finishing time ($p<0.0125$) (Thomas & Motley 1984). The athletes who finished first had the highest levels of myoglobinemia.

Boudou et al. (1987) demonstrated both creatinemia and myoglobinemia in the blood of the participants following a marathon race. They drew the conclusion that these biochemical modifications are the consequences of hydro-mineral losses, muscular necroses and alteration of energetic metabolism with increase of the protein catabolism.

Running a marathon puts a very different constraint on the body compared to AR. Marathons generally last just a few hours, though it is still considered an ultra-endurance event. The participants work at a high percent of VO_{2max}, approximately 75%, during the race (Tanaka & Matsuura, 1984). That equals 67.1 +/- 4.2 ml/kg/min for women and 74.1 +/- 2.6 ml/kg/min for men (Pate et al., 1987; Pollock 1977). In contrast, during AR the relative heart rate averages between 41 and 64 % in a 96-116 hour long race (Lucas et al. 2008). The cause of rhabdomyolysis during a marathon is most likely a metabolic crisis (unbalance between energy intake and output) induced by prolonged exercise (Clarkson, 2007). Our hypothesis is that the same is true for AR.

Exercise and NSAID

The research data on the effects of NSAID (non-steroidal anti-inflammatory drugs) on exercise-induced rhabdomyolysis is limited and inconclusive. It has been shown that NSAID reduce histological evidence of contraction-induced rhabdomyolysis in rabbits (Mishra et al. 1995). O'Grady et al. (1999) found that preadministration of diclofenac significantly reduces quantitative indices of exercise-induced rhabdomyolysis in humans. They examined the effects of prolonged systemic administration of diclofenac sodium (e.g., Voltaren) on objective indices (S-CK levels and muscle biopsies) of exercise-induced muscle damage in humans performing a 20 minute stepping exercise. Their randomized double-blind, placebo-controlled trial showed that preadministration of diclofenac resulted in significantly lower post-/pre-exercise CK ratios ($p=0.02$) compared with the placebo group, as well as significantly reduced quantitative indices of exercise-induced skeletal muscle damage ($p=0.002$).

The opposite has also been shown. The results from one study suggest that diclofenac does not influence muscle damage, but may slightly reduce the associated soreness. A randomized, double blind study showed that diclofenac had no influence on the serum biochemical response to downhill running during 45 minutes, and neither on the overall soreness, but that individual soreness measurements were reduced by diclofenac (Donnelly et al. 1988). The conclusion that a prophylactic dosage of ibuprofen does not prevent CK release from muscle after a strenuous eccentric exercise bout, but does decrease muscle soreness perception and may assist in restoring muscle function, has also been drawn (Hasson et al 1993)

It has also been shown that the risk of exertional rhabdomyolysis leading to renal failure is greatly enhanced when taking analgesics. Mac Serraigh et al. (1979) reported nine cases of acute renal failure caused by rhabdomyolysis in a marathon race. Seven of these runners had

taken analgesics. Seedat et al. (1989) reported four cases of acute renal failure after the Comrades Marathon (approx. 90 km hilly ultra-marathon), all of which had ingested analgesics. Vitting et al. (1986) reported that a 41-year old male had taken naproxen for 1 week before a marathon, and then collapsed during the marathon due to acute renal failure. Clarkson (2007) comes to the conclusion that factors provoking renal failure in cases of exertional rhabdomyolysis in a marathon situation are a pre-existing viral or bacterial infection and/or the use of analgesics and NSAID.

All these previous studies only included, compared to AR, short exercise bouts. It is thus interesting to study the effects of NSAID on rhabdomyolysis after much longer sessions of exercise.

Purpose

The purpose of this study is to examine if a milder form of rhabdomyolysis with myoglobinemia exists during a 48+ hour ultra-endurance adventure race. If such a condition is found to exist, this study wishes to examine further whether there is a relationship with intake of NSAID, if the level of myoglobin in blood is correlated with the finishing time of the race, and what the relationship is between myoglobin levels and the level of the athletes' perceived pain, exertion and performance.

This study is a part of a larger research project at the Åstrand Laboratory of Work Physiology called "Physiology of Adventure Racing" that examines several different physiological effects of ultra-endurance work. See www.gih.se/multisport for further information.

Material and Methods

The study was carried out during the Open Nordic Championship in Adventure Racing in Karlstad, Sweden, at the beginning of May 2008. It is a 48+ hour non-stop adventure race race where teams of four navigate, through a number of check-points, from start to finish. The racers cover approximately 370 km (as the crow flies) by foot, mountain bike, inline, kayaks and ropes. Each team member has to carry a backpack with compulsory gear, weighing approximately 5-7 kg. A team consists of three males and one female, or four males. Teams have to arrange for their own food, but are allowed to get help from a support team at transition areas, approximately every 6-12 hours. A compulsory stop halfway through the race allowed the research team to take measurements and make observations of the five teams participating in the study. The teams that did not participate in the study could use that hour to rest, but otherwise there was no mandatory sleep or rest during the race.

All subjects were volunteers and they received economic compensation for participating. They were fully informed about the procedure, possible discomfort involved, and their right to terminate the experiment at any point. Written informed consent was obtained from all subjects. The design of the study conformed to the Declaration of Helsinki, and was approved by the Regional Ethics Committee in Stockholm, Sweden.

Subject characteristics

20 participants from five teams of four (3 female and 17 male) participated in the study. Table 1 summarizes the mean age, weight and height for each study group. No statistically significant differences existed between groups for age, weight height, exercise time or pre-race heart rate.

All the participants had previously competed in adventure races, but for some it was their first 48+ hour race. Two of the teams were more experienced.

Table 1. Subject characteristics

	NSAID (N=4)	no NSAID (N=16)	p-value
Age (years)	31.0 (s=4.1)	30.7 (s=6.2)	0.929
Weight (kg)	77.3 (s=9.8)	77.3 (s=7.7)	0.999
Height (cm)	173.8 (s=8.2)	180.6 (s=6.4)	0.196
Exercise time (h)	55.5 (s=4.1)	52.7 (s=5.5)	0.299
Heart rate Pre[1] (b/min)	129 (s=16.3)	129 (s=9.8)	0.989

Experimental procedures

Blood sampling

Blood samples for analyses of myoglobin concentration in plasma were taken, by a standard venepuncture technique, from the antecubital vein a few hours before the start of the race (Myo Pre), half-way through the race (Myo Mid) and within 30 minutes of crossing the finish line (Myo Post). Analyses were performed with electrochemiluminescense immunoassay (ECLIA) with measurement interval between 21-3000 µg/L (Myoglobin-P med Modular E170, Roche Diagnostics Ltd, Sverige).

Questionaire

The subjects were required to fill out a survey before each blood sampling. The survey asked if they regularly take any NSAID and if they had taken any within 12 hours of the blood sampling. They were asked to state their level of exertion before the sampling and rate it at the Borg-RPE scale of 6 to 20, 6 being no exertion and 20 being maximal exertion (subjects were given a card explaining the different levels), and also to state their level of muscle pain on the Borg-CR scale of 0 to 10, where 0 is no pain and 10 is maximal pain (Borg G, 1970; Borg G, 2004). At the mid and post race samplings they were also asked to estimate their own performance so far in the race on a scale of 1 to 3, with 1 being “strong, carried extra weight, helped pull team-mates”, 2 being “neither strong nor weak, carried my own” and 3 being “weak, got help from team-mates to carry my weight or was pulled by team-mates. Thus, the rating is related to the team rather than the result of the competition.

[1] Heart rate Pre was recorded before the race during steady state cycling at 175 W

Statistical analysis

All data are presented as mean and standard deviation (s). Significance was accepted at $p<0.05$, and trends were considered at $0.05<p<0.1$. Statistical analysis was done in SPSS. For analyses of differences between groups independent sample t-tests were used, after Levene´s test for equality of variances was performed. For analyses of relationships between variables, Pearson Correlation analysis was used.

Results

None of the subjects withdrew from the study and all finished the race. Therefore all 20 subjects were available for the final analysis.

This was not a randomized controlled study. The subjects themselves choose if they were going to take NSAID, what substance and what amount. Four subjects used NSAID, so the incidence of NSAID use was 20%. They altogether took 18 Voltaren (25 mg) and 11 Panodil (500 mg) spread over the full race. The distribution of NSAID consumption between those four subjects was relatively even, between 5 and 13 tabletts throughout the race. None of the subjects had taken any of the other substances that were asked for in the questionnaire (see Appendix).

The finishing time ranged from 45:29 h to 59:27 h with a mean finishing time of 53:14 h (s=5:10).

There was a significant rise in overall myoglobin at Myo Mid and Myo Post compared with Myo Pre (both $p<0.001$). There was no significant difference between Myo Mid and Myo Post ($p>0.05$).

Diagram 1 shows the results from the myoglobin analyses from both the NSAID and the no NSAID group. There was a statistically significant difference ($p<0.05$) between the two groups for Myo Pre and Myo Post, with the NSAID group having lower myoglobin levels than the no NSAID group. The same trend is true for Myo Mid (Diagram 1).

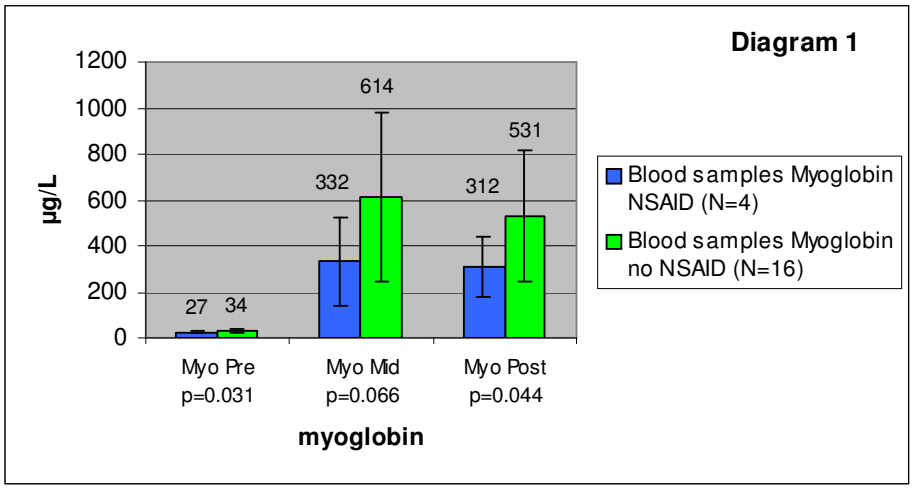

Table 2 displays the means of the perceived exertion, pain and performance, divided into the NSAID and no NSAID group. There was no significant difference between the two groups. However, a Pearson Correlation test displayed interesting correlations between different parameters. The higher the Myo Pre, the higher was the Myo Mid (r=0.610; p=0.010) and the Myo Post (r=0.655; p=0.004). A higher Myo Pre (and thus a higher Myo Mid and Myo Post) was correlated to a shorter finishing time of the race (r=-0.512; p=0.026), as well as a lower HR post (r=-0.484; p=0.034). A high Myo Pre was also correlated to a lower perceived degree of exertion Post (r=-0.673; p=0.003), a higher performance Mid (r=-0.472; p=0.038), and a lower level of pain Post (r=-0.455; p=0.44). The older a racer, the higher was the Myo Post level (r=-0.514; p=0.021).

So our results indicate that higher levels of myoglobin before and during the race have a positive effect on race results, perceived pain and exertion during the race, as well as percieved performance.

Table 2. Answers from survey

	NSAID (N=4)	no NSAID (N=16)	p-value
Exertion mid	15.50 (s=1.3)	14.63 (s=2.0)	0.512
Pain mid	3.75 (s=1.5)	3.13 (s=1.2)	0.517
Performance mid	2.00 (s=0.8)	1.69 (s=0.5)	0.666
Exertion post	15.75 (s=3.1)	16.00 (s=2.7)	0.796
Pain post	3.75 (s=1.3)	4.81 (s=1.8)	0.308
Performance post	1.75 (s=1.0)	1.75 (s=0.7)	0.374

Discussion

This is an interesting area of study, and very relevant to the sport of adventure racing, since it is so common to ingest some type of analgesic, usually NSAID, during races. The reasons to do so are of course individual, but during long races like these it is not so uncommon to develop different kind of musculoskeletal injuries and still want to continue the race. It is also common to already have some type of musculoskeletal problem that you know will hurt you during the race, but you still do not want to give up racing. An easy way to continue to race then is to ingest analgesics. But the research on the subject is very limited, and the effects of the ingested analgesic is unknown to the racer.

The results of this study are similar to those of O´Grady et al. (1999), who found that preadministration of diclofenac reduced exercise-induced muscle damage. Mishra et al. (1995) also showed that NSAID reduce histological evidence of contraction-induced rhabdomyolysis. Donnelly et al. (1988), on the other hand, showed that diclofenac does not influence muscle damage. And the same was shown for Ibuprofen by Hasson et al. (1993).

Thus, the results of other studies of NSAID in relation to muscle damage and release of muscle proteins seem to both contradict and support the main conclusions of this study. There may be several reasons why our results slightly differ from earlier studies, namely the time of exertion of participants in our study was longer compared to the other studies, and intensity of the work that have been performed in each study was different. Also, this is one of few studies that examine the level of myoglobin-, instead of CK-release into the blood. Maybe there is a difference in what triggers or prevents release of CK compared to Myoglobin? And maybe it

is so that intensity is worse than duration, which would explain why some of the other studies have contradictory results to our study. AR has a very long duration, but the intensity is not that high. After a triathlon race, with usually higher intensity than AR, the average peak level of myoglobin was 842 ng/ml over a 24 hour period (Thomas & Motley 1984).

However, our results also indicate that higher levels of myoglobin before and during the race have a positive effect on race results, perceived pain and exertion, as well as perceived performance. That higher levels of myoglobin is correlated with a better race result has been shown before (Thomas & Motley 1984). They showed that a significant correlation existed between average S-Mb and finishing time after a triathlon race ($p<0.0125$), results very similar to those of this study ($p=0.026$). The athletes who finished first had the highest levels of myoglobinemia.

So, it seems as if intake of NSAID decreases the risk for rhabdomyolysis and the release of myoglobin into the blood, which should be positive from a physiological view. But from a strict racing performance view it seems as if high myoglobin levels would be beneficial, both for race results but also for the athlete's comfort and enjoyment during the race. Thus, it might be beneficial to have a higher level of myoglobin in the blood, and thus a milder form of rhabdomyolysis.

One might speculate that the correlation between better race results and higher myoglobin levels has something to do with the age of the racers. The older a racer, the higher was the myoglobin level ($r=-0.514$; $p=0.021$), and older racers are usually more experienced, and thus might perform better in an event were diverse technical skills are required. A lower heart rate (HR Post) was also correlated to a higher myoglobin level ($r=-0.484$; $p=0.034$). Older people usually have lower hear rates and that would support the hypothesis that older racers where the ones with better race results.

One of the limitations with this study is that the intake of NSAID was not randomized; athletes themselves that decided if, and what dose, of NSAID to consume. The number of subjects in the NSAID group was small relative to the no NSAID group and may have caused our results to show correlations that may or may not exist in larger and more proportional groups.

It is tricky to yet give out guidelines to AR athletes about what the effect of NSAID intake really has on their race results and well-being. But the results in this study are interesting and do point towards an effect of NSAID on myoglobin levels, and of myoglobin levels on race results. We suggest further studies under race-like conditions with larger population samples and a controlled intake of NSAID.

Conclusion

The results from this study indicate the existence of a mild form of rhabdomyolysis during a 48 hour adventure race and demonstrate a positive effect of NSAID on the level of myoglobin in the blood. So it confirms the results of some earlier studies, that have also shown that the degree of rhabdomyolysis is lower after NSAID intake, but contradicts the results of others. So the research data on the effects of NSAID on exercise-induced rhabdomyolysis is still inconclusive.

The interesting outcome of this study is that intake of NSAID seem to lower the muscle breakdown and the release of myoglobin into the blood, which should be positive. But on the other hand, it seems as if high myoglobin levels have a positive effect on actual race results as well as the athletes' perceptions of level of pain, exertion, and performance. Thus, it might be beneficial for final race results and for athletes' perceptions to have a higher level of myoglobin in the blood, and thus a milder form of rhabdomyolysis.

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Appendix

Dessa frågor är till för att undersöka hur musklerna påverkas vid denna typ av långvarig ansträngning.

1. Tar du regelbundet någon av följande mediciner?

NSAID (t.ex. Alvedon, Voltaren, Pronaxen: Yes No

Om "Yes" namn och mängd:_____

SSRI-preparat: Yes No

Om "Yes" namn och mängd:_____

Kosttillskott med kreatinin: Yes No

Om "Yes" namn och mängd:_____

Statiner (blodfettssänkande): Yes No

Om "Yes" namn och mängd:_____

2. Har du nyligen tagit (inom 12 h) någon av följande mediciner?

NSAID (t.ex. Alvedon, Voltaren, Pronaxen: Yes No

Om "Yes" namn och mängd:_____

SSRI-preparat: Yes No

Om "Yes" namn och mängd:_____

Kosttillskott med kreatinin: Yes No

Om "Yes" namn och mängd:_____

Statiner (blodfettssänkande): Yes N

Om "Yes" namn och mängd:_____

3. Skatta din ansträngning strax innan provtagningstillfället på nedanstående skala (sätt ett kryss i ruta till höger).

6	Ingen ansträngning alls	
7		
8		
9	Mycket lätt	
10		
11	Ganska lätt	
12		
13	Något ansträngande	
14		
15	Ansträngande	
16		
17	Mycket ansträngande	
18		
19	Extremt ansträngande	
20	Maximal ansträngning	

4. Skatta din muskelsmärta i arbetande muskler de senaste tre timmarna innan provtagningstillfället på nedanstående skala (sätt kryss i ruta till höger).

0	Ingen alls	
0,5	Extremt svag (knappt kännbar)	
1	Mycket svag	
2	Svag (lätt)	
3	Måttlig	
4		
5	Stark (kraftig)	
6		
7	Mycket stark	
8		
9		
10	Extremt stark (nästan max)	

5. Skatta din och övriga lagmedlemmars prestation de senaste 6 timmarna i förhållande till resten av laget (skriv namn i ruta till höger).

1	Stark, fick bära extra drog lagkamrater.	
2	Varken stark eller svag, bar sitt eget.	
3	Sliten, fick hjälp att bära, blev dragen	