Research in Sports Medicine: An International Journal
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gspm20

A Prospective Cohort Study of Acute Kidney Injury in Multi-stage Ultramarathon Runners: The Biochemistry in Endurance Runner Study (BIERS)

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Published online: 21 Mar 2014.

To cite this article: Grant S. Lipman, Brian J. Krabak, Brandee L. Waite, Sarah B. Logan, Anil Menon & Garrett K Chan (2014) A Prospective Cohort Study of Acute Kidney Injury in Multi-stage Ultramarathon Runners: The Biochemistry in Endurance Runner Study (BIERS), Research in Sports Medicine: An International Journal, 22:2, 185-192, DOI: 10.1080/15438627.2014.881824

To link to this article: http://dx.doi.org/10.1080/15438627.2014.881824

Research in Sports Medicine, 22:185–192, 2014

ISSN: 1543-8627 print/1543-8635 online
DOI: 10.1080/15438627.2014.881824

Routledge
Taylor & Francis Group

A Prospective Cohort Study of Acute Kidney Injury in Multi-stage Ultramarathon Runners: The Biochemistry in Endurance Runner Study (BIERS)

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The purpose of the study was to evaluate the prevalence of acute kidney injury (AKI) during a multi-stage ultramarathon foot race. A prospective observational study was taken during the Gobi 2008; Sahara 2008; and Namibia 2009 RacingThePlanet 7-day, 6-stage, 150-mile foot ultramarathons. Blood was analyzed before, and immediately after stage 1 (25 miles), 3 (75 miles), and 5 (140 miles). Creatinine (Cr), glomerular filtration rate (GFR), and incidence of AKI were calculated and defined by RIFLE criteria. Thirty participants (76% male, mean age 40 + 11 years) were enrolled. There were significant declines in GFR after each stage compared with the pre-race baseline ($p < 0.001$), with the majority of participants (55–80%) incurring AKI. The majority of study participants encountered significant renal impairment; however, no apparent cumulative effect was observed,

Received 2 September 2013; accepted 8 December 2013
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with resolution of renal function to near baseline levels between stages.

KEYWORDS ultramarathon, acute kidney injury, multi-stage, recovery from exercise

INTRODUCTION

Ultramarathon events of distances greater than the traditional 26.2 miles of a marathon are increasing in popularity, attracting more than 70,000 annual participants worldwide (Krabak, Waite, & Schiff, 2011). Considerable literature has documented alterations in renal function in healthy race finishers (Irving, Noakes, Burger, et al., 1990; Page, Reid, Speedy, Mulligan, & Thompson, 2007) as well as those seeking medical care (Irving et al., 1991; Reid & King, 2007). The etiology of renal dysfunction is thought to be multi-factorial, with dehydration, subsequent reduced renal perfusion (Neumayr et al., 2003), and decreased glomerular filtration as contributors. A 'perfect storm' of insults such as heat stress, dehydration, underlying myopathy, and non-steroidal anti-inflammatory drug (NSAID) use in some combination may combine to result in functional injury, although acute renal failure in this population is rare (Clarkson, 2007). Multi-stage events have the potential for cumulative kidney stress; however, the opportunity for potential recovery after each day of racing may provide a similar injury pattern as observed in endurance single stage races, where a transient decrease in renal function would subsequently resolve (Irving, Noakes, Raine, & Van Zyl Smit, 1990; Page et al., 2007). The purpose of this study is to determine the prevalence of renal injury in multi-stage ultramarathon runners and whether there is a cumulative effect to renal injury over the course of a race.

METHODS

Setting and Participants

The RacingThePlanet events (www.4deserts.com) are 7-day, 6-staged 150-mile (250 km) ultramarathon foot races through diverse wilderness terrain with wide fluctuations of temperature, humidity, and topography. These stage races have competitors running four sequential 25 miles (40 km) days, a fifth day of 40 miles (80 km), finishing with the last day of 10 miles (16 km) – with no rest days in between. Participants carry all their own gear for the race, including a minimum of 2000 calories/day, and are offered 1.5 liters water per 10–12 km along the course. The study venues included the 2008 Gobi Desert, China; 2008 Sahara Desert, Egypt; and 2009 Namibian desert. All competitors in a RacingThePlanet event were given the opportunity to enroll at race

registration. Approval was obtained from institutional review boards at Stanford University School of Medicine, University of Washington Medical Center, and University of California Davis School of Medicine.

Procedures

Participants were enrolled the day before the race with documentation of racer demographics, including sex, age, height, weight and BMI. Blood samples were obtained from each participant the morning prior to the start of, and within minutes of race completion for each of the following stages: 1 (25 miles [40 km]), 3 (75 miles [120 km]) and 5 (140 miles [240 km]). Blood samples were obtained via lancet and capillary collection tube, (Mock, Morrison, & Yatscoff, 1995) then measured onsite immediately after collection using an iSTAT point-of-care analyzer (Abbott; East Windsor, NJ) per manual instructions.

Analysis

A descriptive analysis was performed of racer demographics. RIFLE criteria (Bellomo, Ronco, Kellum, Mehta, & Palevsky, 2004) were used to quantify acute kidney injury (AKI), with criteria calculated by the value that led to the worst possible classification (Hoffman et al., 2013). Measured creatinine (Cr) and glomerular filtration rate (GFR) were compared to pre-race baseline values with risk (R) defined as Cr 1.5 times normal or a decrease of GFR by 25–49%, and injury (I) Cr twice normal or a decrease of GFR by 50–75%. GFR was calculated by the Cockcroft-Gault formula in mg/dl = (140 – age) × mass (kg) [× 0.85 if female] / 72 × serum creatinine (mg/dl) (Cockcroft & Gault, 1976). A paired t-test and Wilcoxon signed rank test were used for analysis, and all statistical significance was considered at $p < 0.05$. All analysis was by SPSS (SPSS version 19.0).

RESULTS

A total of 34 subjects were enrolled in the study over three races. Four participants refused participation prior to testing, and they were not included in the final analysis. Of the 30 participants undergoing testing, seven (23.3%) were from the Sahara, 10 (33.3%) from the Gobi, and 13 (43.3%) from the Nambian races. There were 29 participants with complete data sets through stage 1, 15 through stage 3, and 14 through to the end of stage 5. As all three races had approximately equal distances, caloric, and logistical demands, all the participants were combined into one cohort for analysis. The characteristics of the study participants are described in Table 1.

TABLE 1 Study participant demographics

	N	Mean (± SD)	Range
Sex (male)	30	23 (76%)	
Age (years)	30	39.6 ± 10.6	25 – 66
Height (inches)	17	69.2 ± 3.9	58 – 75
Body Weight (lbs)	17	158.8 ± 36.8	75 – 235
BMI (lbs/inches^2)	17	23.18 ± 4.3	11 – 31

BMI = body mass index; SD = standard deviation

Each of the stages saw similar non-statistically significant increases in serum creatinine and decreases in participants' GFR between the start and end. Compared with pre-race baseline there were significant decreases in GFR over each stage ($p < 0.001$) (Tables 2 and 3). All racers experienced almost

TABLE 2 Renal function results of all pre-race and post-race for stages 1, 3, and 5

	Pre-race Stage 1 Mean ± SD (range)	Stage 1 Finish Mean ± SD (range)	Stage 3 Finish Mean ± SD (range)	Stage 5 Finish Mean ± SD (range)
N	30	29	15	14
Cr (mg/dl)	1 ± 0.2 (0.7–1.4)	1.4 ± 0 .4 (0.7–2.4)	1.4 ± 0.4 (1–2.4)	1.4 ± 1.3 (1–2.2)
GFR (mg/dl)*	103 ± 21.6 (59–149)	75 ± 18.6 (49–116)	73 ± 17.7 (49–106)	72 ± 19.7 (42–106)
ΔGFR (mg/dl) (95% CI)		28 ± 25 (19–38)[a]	30 ± 20.1 (18–41)[b]	31 ± 17.5 21–41)[c]

Cr = creatinine; GFR = glomerular filtration rate; SD = standard deviation; ΔGFR = change in GFR as compared to pre-race baseline; * = GFR calculated only on the participants with recorded weights; CI = confidence intervals; [a] $p < 0.001$ when pre-race baseline compared to post-race stage 1; [b] $p < 0.001$ when pre-race baseline compared to post-race stage 3; [c] $p < 0.001$ when pre-race baseline compared with post-race stage 5.

TABLE 3 Renal function results pre-race and post-race for stage 1, 3, and 5 finishers

	Pre-race Stage 1 Mean ± SD (range)	Stage 1 Finish Mean ± SD (range)	Stage 3 Finish Mean ± SD (range)	Stage 5 Finish Mean ± SD (range)
N	14	13	14	14
Cr (mg/dl)	0.9 ± 0.2 (0.7–1.2)	1.4 ± 0.4 (0.7–2.1)	1.3 ± 0.4 (1–2.4)	1.4 ± 0.3 (1–2.2)
GFR (mg/dl)	102.7 ± 17.3 (80.9–141.2)	76.6 ± 18.3 (53.9–115.5)	74.5 ± 17.2 (49.2–105.9)	71.8 ± 19.6 (41.5–105.9)
ΔGFR (mg/dl) (95% CI)		32.5 ± 18.9[a] (3–76.9)[a]	28.1 ± 20 (–7.4–84)[b]	30.9 ± 17.5 (–16.2–17.5)[c]

Cr = creatinine; GFR = glomerular filtration rate; SD = standard deviation; ΔGFR = change in GFR as compared to pre-race baseline; CI = confidence intervals; [a] $p = 0.002$ when pre-race baseline compared to post-race stage 1, $n = 11$; [b] $p = 0.002$ when pre-race baseline compared to post-race stage 3; [c] $p < 0.001$ when pre-race baseline compared with post-race stage 5.

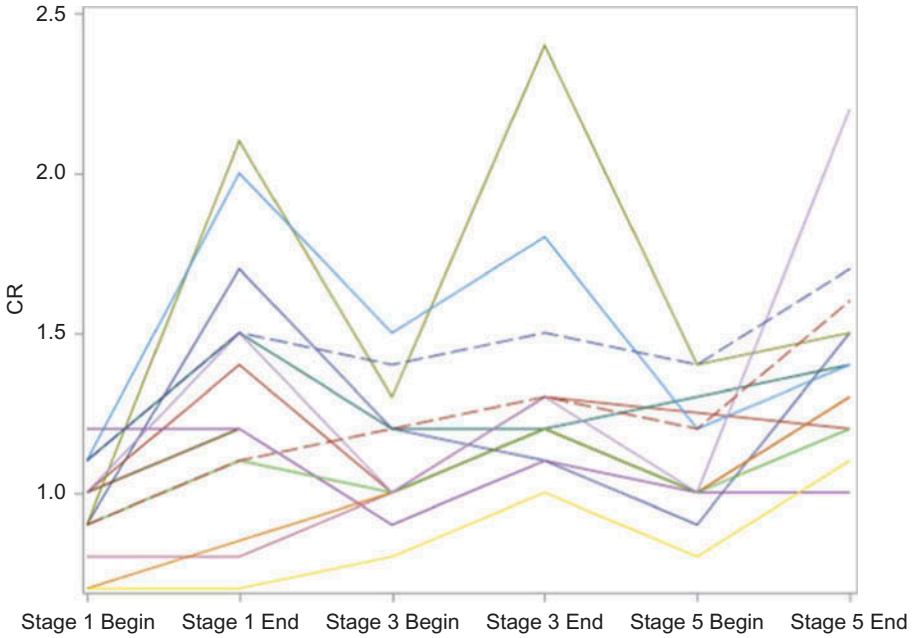

FIGURE 1 Changes in creatinine over the course of the race.

CR = creatinine (mg/dl). Each line represents an individual study participant who completed all days of data collection.

complete resolution of creatinine to near baseline values by the beginning of each successive stage of testing (Figure 1). The majority of study participants suffered some form of renal impairment, with incidence of pre-defined AKI on stage 1: risk = 13 (45%) and injury = 3 (10%); stage 3: risk = 10 (67%) and injury = 2 (13%); and stage 5: risk = 8 (57%) and injury = 1 (7%).

DISCUSSION

This study is the first, to the authors' knowledge, that defines acute kidney injury prevalence and severity a multi-stage ultramarathon. The majority of participants (55–85%) measured in the study had acute kidney injury per the RIFLE criteria. This was greater than after a standard marathon (40%) (McCullough et al., 2011), and a continuous ultramarathon (34%) (Hoffman et al., 2013). The observed high prevalence of AKI was consistent over the three stages studied. It is reasonable that the long duration of exercise and intense exertions by runners carrying a week's supply of food and gear in wilderness terrain may have increased the risk for developing injury.

While study participants experienced a significant decrease in GFR over the course of stages compared with starting values, renal function returned to

near baseline levels prior to the beginning of each successive stage. This resolution pattern appears similar to continuous single-day ultramarathon studies that documented resolved renal impairment within 24 to 72 hours of finishing (Irving et al., 1990; McCullough et al., 2011; Page et al., 2007). We speculate that normalized renal function prior to the start of the following stage reflected adequate opportunity for rehydration and recovery of renal function – without apparent cumulative effect.

Despite the current study findings of resolution of GFR for each stage, the long-term clinical repercussions of these resolved renal abnormalities are unknown. Additionally, the findings of significant acute kidney injury per the RIFLE criteria raises concern for potential exacerbation of renal injury with concurrent NSAID ingestion. It has been reported that up to 75% of ultra-endurance athletes use NSAIDs during competition (Wharam et al., 2006), and concurrent use has been associated with a greater increase in hospitalization and acute renal failure than in matched controls during an ultramarathon (Bruso et al., 2010). Further prospective studies are needed to better understand the impact of NSAIDs on the multi-stage running athlete.

The use of sophisticated diagnostic equipment in a wilderness environment to collect biochemical data was both a strength and limitation of this study. As the attrition rate for complete data collection was approximately 50% and the number of participants with complete datasets was small, it is possible that athletes who dropped out of the study were better able to regulate kidney function, affecting our statistical significance. In addition, the logistical challenges of a prospective study throughout a multi-stage ultramarathon limited the gathering of data to specific stages, allowing for the possibility that the non-studied stages' results may have altered observed findings. While the direction of trends was consistent among the study participants, the small number of participants may not have been fully representative of the prevalence of disease.

There was no control for variables, including NSAID use, quality or quantity of caloric intake, as well as the athletes' option to stop at an aid station prior to the finish line on stage 5 for rest and/or rehydration, all which may have affected results. Other factors possibly altering outcomes could include ambient temperature and actual fluid ingestion. Inter-race data were combined as a single cohort as the distances traveled in the each race were approximately equal; however, as the topography and environmental conditions varied between the study locations, this assumption may have led to disparate results.

CONCLUSION

As participation in ultramarathons around the world continues to increase, athletes should be informed about the potential for deleterious effects on kidney function. While results showed statistically significant renal function

impairment in the studied multi-stage ultramarathon runners, this appeared to recover with rest and rehydration between stages. Future studies should examine the relationship between sex, age, and training/fitness level and ultra-running with regard to kidney function, renal injury, and possible exacerbation with NSAID use.

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