The Journal of Emergency Medicine, Vol. 56, No. 2, pp. 177–184, 2019
Published by Elsevier Inc.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.10.026

Selected Topics: Sports Medicine

PREDICTED RISK FOR EXACERBATION OF EXERCISE-ASSOCIATED HYPONATREMIA FROM INDISCRIMINATE POSTRACE INTRAVENOUS HYDRATION OF ULTRAMARATHON RUNNERS

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☐ **Abstract—Background: Asymptomatic or mildly symptomatic exercise-associated hyponatremia (EAH) can be exacerbated by aggressive hydration. Objective: This work predicts the percentage of athletes at risk for exacerbation of EAH from indiscriminate hydration after an ultramarathon. Methods: Postrace serum sodium, creatinine, creatine kinase (CK), and urea nitrogen concentrations were determined for 161-km ultramarathon participants. Body mass was measured prior to and immediately after the race. Incidents when serum CK was > 20,000 U/L or creatinine ≥ 1.5 times estimated baseline were considered to be "at risk for receiving I.V. hydration" if presenting to a hospital. Those with EAH without body mass loss during the race were considered "overhydrated" and "at risk for EAH exacerbation." Results: Among 627 finishers, 16 (2.6%) were at risk for EAH exacerbation. Considering 421 observations at risk for receiving I.V. hydration, 16 (47.1%) of the 34 observations with EAH were at risk for EAH exacerbation. Among those at risk for receiving I.V. hydration and with EAH, serum urea nitrogen and creatine concentration as a multiple of estimated baseline were lower ($p < 0.05$) for those at risk for EAH exacerbation, compared with those without overhydration, but there were no clinically useful laboratory findings to distinguish these two groups due to considerable overlap of values. Conclusions: Whether in the field or hospital setting, I.V. hydration of an athlete after an ultramarathon carries a notable risk for exacerbating EAH, so clinicians should use caution when hydrating athletes after endurance events. Published by Elsevier Inc.**

☐ **Keywords—acute kidney injury; creatine kinase; creatinine; dehydration; endurance exercise; rhabdomyolysis**

INTRODUCTION

Athletes will often transiently meet the criteria for risk of acute kidney injury (AKI) after completion of an ultramarathon, with documented incidence being 34–85% in 100-km and 161-km single-stage and 250-km multistage ultramarathons (1–6). Virtually all of these cases are recognized only as a result of research, resolve without specific intervention, and seem to not result in long-term health sequalae (2). Yet, athletes can end up seeking medical attention for concern over kidney injury and various other maladies after ultra-endurance events (7,8). In the emergency department (ED) or hospital setting, the elevated serum creatinine concentrations and high serum creatine kinase (CK) concentrations from exercise-associated rhabdomyolysis, often over 20,000 U/L after 161-km ultramarathons, may prompt concern about AKI among many clinicians (1,2,7,9–12). As a result, medical providers will often implement aggressive intravenous (I.V.) hydration with isotonic or hypotonic fluids because this is the core management of rhabdomyolysis and impending kidney failure (13–21).

Received: 3 August 2018; Final submission received: 16 October 2018;
Accepted: 18 October 2018

This seems to be the case even though the predicted risk of kidney failure from exertional rhabdomyolysis has been shown to be low, and it has been suggested that such aggressive treatment of rhabdomyolysis may be unwarranted (2,21–26).

Exercise-associated hyponatremia (EAH) is another condition that has been quite common in endurance and ultra-endurance events. EAH is defined by a serum sodium concentration below the normal reference range for the laboratory, occurring during or up to 24 h after physical activity (27). Two compilation studies from multiple events ranging in completion times from ~3 to 30 h demonstrated that EAH occurred in an average of 7% and 15% of the race finishers (28,29). Fortunately, most athletes with EAH are asymptomatic, and serum sodium concentration tends to self-correct if excessive fluid intake is avoided while this correction is allowed to occur. It seems that those who are overhydrated (i.e., hypervolemic hyponatremia) are at risk for becoming symptomatic from EAH (28,30). Early symptoms of EAH are often mild or nonspecific and could be mistaken for dehydration, particularly because oliguria is common in EAH because arginine vasopressin (AVP) is known to be involved in its pathogenesis, and symptoms can rapidly progress to loss of consciousness or seizure an hour or more after cessation of exercise (27,30–37). Concern expressed that additional hydration efforts prior to AVP secretion has been suppressed in asymptomatic or mildly symptomatic EAH cases will result in the development of potentially life-threatening EAH, has been supported by several case reports (34,37–43). In fact, isotonic fluids can cause further lowering of serum sodium concentration in EAH, and there is considerable evidence that symptomatic cases of EAH treated with I.V. isotonic fluids may, at the least, have worsening of neurological symptoms or delayed recovery compared with cases receiving hypertonic saline (42,44–47). Proper treatment of EAH involves fluid restriction and I.V. (or oral, when possible) boluses of hypertonic saline (27,48). Nonetheless, it is not unusual for patients with known EAH to be managed with isotonic fluids during transport, in the ED, and in the hospital setting (30,44,46,49–51).

Thus, these two conditions that are common in ultra-endurance events are treated with opposing interventions, and the proper intervention for one condition could exacerbate the other. At least in the ED and hospital setting, serum sodium concentration can be monitored, and hypertonic saline can generally be available to promptly reverse hyponatremia symptoms that might result from hydration efforts in treating rhabdomyolysis. In contrast, the provider caring for an athlete after an event and the for-purchase on-demand I.V. hydration services, which have developed a presence at ultra-endurance competitions in the United States, do not typically perform blood studies prior to provision of postevent hydration, nor do they necessarily have the capacity to properly manage symptomatic EAH (39,52). Emergency medical transport services will also not typically have the option to assess serum sodium concentration prior to institution of hydration efforts. As such, legitimate concern has been raised about the likelihood of inducing or exacerbating symptomatic EAH from such indiscriminate hydration practices (38–41,52).

The intent of the present analysis was to 1) predict the percentage of athletes at risk for exacerbation of EAH if indiscriminately receiving I.V. isotonic or hypotonic fluids after an ultramarathon without attention to whether or not they are hyponatremic, and 2) examine if there are any distinguishing features within the typical laboratory data that would identify, among those athletes presenting to the ED or hospital after an ultramarathon with hyponatremia, the ones who are at risk for exacerbation of EAH from aggressive hydration implemented over concern about rhabdomyolysis and potential AKI. Postrace blood analyses and body mass change data collected at 161-km ultramarathons were used in the analyses.

METHODS

Study Design and Setting

The data presented herewith are from observational studies at the Western States Endurance Run (WSER), a 161-km point-to-point foot race that is almost entirely on single-track mountain trails with 5500 m of cumulative climb and 7000 m of cumulative descent. Participants have a 30-h time limit for completion. Other details of the race have been provided elsewhere (53–55). Data were collected with approval from the institutional review board at the VA Northern California Health Care System with a waiver of consent.

Study Participants

Study participants were finishers of the 2011, 2012, and 2014 WSER who were willing to provide a blood sample after finishing the race. To enhance the recognition of characteristics that might differentiate between hyponatremic athletes who are and are not overhydrated while also being at risk for AKI, data from three finishers and three nonfinishers who were hospitalized after the 2009 and 2013 events with concern over AKI and concomitant EAH were included in some analyses. These cases have been previously described (7,30). Their admission laboratory data were used in this analysis, and for the nonfinishers, the last body mass measurement on the

course prior to dropping out was used to determine body mass change.

Measurements

Identical methodology was used to collect the data at the 2011 through 2014 WSERs. Runners were weighed during registration in the morning on the day prior to race start. Body mass was also measured at multiple locations on the course and immediately upon completion of the race. Calibrated battery-operated digital scales (model 349KLX; Health o Meter, Boca Raton, FL) placed on solid level surfaces were used for all measurements, with the runner clothed in running wear and shoes. Care was taken to assure that other items, such as jackets, waist packs, and hydration vests, were removed and nothing was in the runner's hands. Within a few minutes after finishing the race, runners willing to provide a blood sample had blood drawn from an antecubital vein into heparinized tubes while they were seated. Analyses for serum sodium, creatinine, urea nitrogen, and CK concentrations were performed by a clinical laboratory.

Definitions

EAH. The lower limit of normal for serum sodium concentration was 135 mmol/L for the clinical laboratory performing the blood analyses. Therefore, EAH was defined by values below 135 mmol/L.

At risk for receiving I.V. hydration. Although the practice is not well supported in the population of endurance athletes, elevated serum creatinine concentrations and serum CK concentrations over 20,000 U/L have been considered reason for aggressive hydration efforts (20,23,56). Therefore, the present study considered that meeting either criteria placed the athlete "at risk for receiving I.V. hydration" if seen in an ED or hospital. The postrace serum creatinine concentration was considered elevated when high enough to meet the "risk" or worse criteria of the RIFLE (Risk, Injury, Failure, Loss and Endstage kidney disease) criteria for AKI (57). The "risk" criteria are defined by a serum creatinine at least 1.5 times baseline creatinine. Because blood was not taken prior to the run, baseline serum creatinine concentration was estimated by first determining an expected baseline glomerular filtration rate, using 100 mL/min when age was ≤40 years and 140 minus age for those >40 years of age (58). This expected baseline glomerular filtration rate, combined with athlete age and sex date, were then used in the "modification of diet in renal disease" equations to back-calculate expected baseline serum creatinine concentration (59). The postrace serum creatinine concentration for each individual was then calculated as a multiple of their estimated baseline serum creatinine concentration.

Overhydration. In this study, "overhydration" was defined as no loss of body mass between race registration and race finish (or last on-course body mass measurement in nonfinishers). Owing to endogenous substrate use, release of water bound with glycogen, and the production of water during substrate metabolism, some mass loss is required to avoid overhydration in a 161-km ultramarathon (60–63).

At risk for EAH exacerbation. It has been suggested that the athletes with a lack of body mass loss from race registration are vulnerable to becoming symptomatic with EAH (28,30). Also, it is presumed that asymptomatic or mildly symptomatic hypervolemic hyponatremic athletes are vulnerable to becoming symptomatic if aggressively hydrated, as has been supported by case reports (34,37,42,43). Thus, those observations of EAH without body mass loss from measurement at race registration were considered "at risk for EAH exacerbation."

Analysis

Those cases at risk for receiving I.V. hydration without EAH, those at risk for receiving I.V. hydration with EAH and without overhydration, and those at risk for receiving I.V. hydration and at risk for EAH exacerbation were identified. Laboratory values and body mass change were then compared among these three groups with the Kruskal–Wallis test followed by Dunn multiple comparison test when an overall significant effect was identified since the variables were generally found to be skewed by the D'Agostino-Pearson test. Statistical significance was set at $p < 0.05$.

RESULTS

Postrace blood analysis and body mass change data were available for 627 finishes (585 unique individuals) at the 2011, 2012, and 2014 races among a total of 922 race finishes across these 3 race years. Of these observations, 35 (5.6%) had EAH and 16 (2.6%) had EAH and overhydration (i.e., at risk for EAH exacerbation).

With the inclusion of the additional three finishers and three nonfinishers from 2009 and 2013 who were hospitalized after the race with EAH, these 633 observations were accounted for by 588 unique individuals. Figure 1 displays the distribution of serum creatinine as a multiple of estimated baseline relative to serum CK concentration among this group. Serum CK concentration ranged from 1473 to 219,700 U/L, and was over 20,000 U/L in 288 (45.5%) observations. Serum creatinine concentration was at least 1.5 times the estimated baseline in 231 (36.5%) observations.

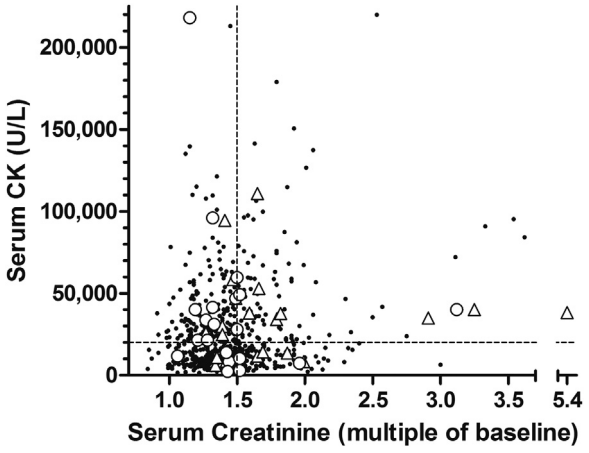

Figure 1. Distribution of serum creatinine as a multiple of estimated baseline relative to serum creatine kinase (CK) concentration among the 633 observations. The open triangles represent 21 incidents of exercise-associated hyponatremia (EAH) without overhydration, and the open circles represent 20 incidents of EAH with overhydration (at risk for EAH exacerbation). The dashed lines demarcate common cut-off values for concern over acute kidney injury.

There were 421 (66.5%) observations in which either post-race serum creatinine concentration was at least 1.5 times the estimated baseline value or serum CK concentration was over 20,000 U/L (i.e., at risk for receiving I.V. hydration). Within that group of 421 observations, there were 34 observations of EAH, of which 16 (47.1%) were overhydrated (i.e., at risk for EAH exacerbation).

Table 1 compares characteristics of those considered at risk for receiving I.V. hydration without EAH, those at risk for receiving I.V. hydration with EAH and without overhydration, and those at risk for receiving I.V. hydration with EAH and with overhydration (i.e., at risk for EAH exacerbation). The two groups with EAH were significantly different for serum creatinine concentration as a multiple of estimated baseline ($p < 0.05$) and serum urea nitrogen concentration ($p < 0.05$). But, examination of the interquartile ranges showed considerable overlap between groups for both laboratory measurements.

DISCUSSION

The athletes most at risk for becoming symptomatic with EAH are hypervolemic (28,30). It is also believed that it is those with hypervolemic hyponatremia in which provision of postrace I.V. isotonic or hypotonic fluids is most likely to exacerbate mild or asymptomatic EAH (26,38–41). Thus, to predict the percentage of athletes at risk for exacerbation of EAH from indiscriminate I.V. hydration, this work examined the incidence of concomitant EAH and overhydration among 627 161-km ultramarathon finishes. In this sample, the overall incidence of EAH was 5.6%, and EAH combined with overhydration was present 2.6% of the time. Prior compilation studies of 161-km ultramarathons, 250-km multistage ultramarathons, and events ranging from marathon run to Ironman triathlon durations have found the overall incidence of EAH to vary widely between 7% and 15%, but the incidence of EAH combined with overhydration was small and within a narrow range of 3.2% to 4.0% (28,29,64). Thus, the present work is consistent with prior studies, and it is suggested that the incidence of EAH combined with overhydration is small at around 3–4% across various endurance and ultra-endurance activities. Nonetheless, although the percentage of athletes at risk for exacerbation of EAH from indiscriminate postevent I.V. hydration is low, there is indeed a meaningful risk with potentially high consequences, which should be considered prior to I.V. hydration efforts. This is particularly noteworthy if the

Table 1. Comparison of Body Mass Change and Post-Race Laboratory Values Among 3 Groups Meeting the Criteria for Being at Risk for Receiving I.V. Hydration*

Characteristic	Group		
	At Risk for I.V. Hydration + No EAH n = 387	At Risk for I.V. Hydration + EAH + No Overhydration n = 18	At Risk for I.V. Hydration + At Risk for EAH Exacerbation n = 16
Body mass change (%)	−0.6 (−2.2 to 0.8)	−1.8 (−3.0 to −0.7)†	1.9 (0.7 to 2.9)†‡
Serum sodium (mmol/L)	140 (138 to 142)	133 (131 to 134)†	133 (131 to 134)†
Serum creatinine (mg/dL)	1.3 (1.2 to 1.5)	1.5 (1.2 to 1.8)	1.2 (1.1 to 1.4)
Serum creatinine (multiple of estimated baseline)	1.5 (1.3 to 1.7)	1.7 (1.5 to 1.9)	1.4 (1.3 to 1.5)‡
Serum urea nitrogen (mg/dL)	26 (21 to 34)	35 (26 to 42)	21 (17 to 37)‡
Serum CK (U/L)	26,300 (15,100 to 43,300)	36,300 (22,140 to 48,395)	36,854 (21,400 to 48,550)

EAH = exercise-associated hyponatremia; CK = creatine kinase; I.V. = intravenous.
One group did not have EAH (at risk for I.V. hydration + no EAH), one group had EAH without overhydration (at risk for I.V. hydration + EAH + no overhydration), and the other group had EAH with overhydration (at risk for I.V. hydration + at risk for EAH exacerbation). Data are reported as median and interquartile range.
* Serum creatinine concentration was at least 1.5 times estimated baseline or serum CK concentration was > 20,000 U/L.
† $p < 0.05$ compared with at risk for I.V. hydration + no EAH group.
‡ $p < 0.05$ compared with at risk for I.V. hydration + EAH + no overhydration group.

necessity of the intervention is questionable, as may often be the case with postevent I.V. hydration (2,21,23–26).

This work also predicted the percentage of athletes at risk for exacerbation of EAH among those presenting to the ED or hospital after finishing a 161-km ultramarathon. It was found that among those who would likely receive I.V. hydration and were also hyponatremic, there was a 47.1% chance that they were also overhydrated. That is, nearly half of those who would likely receive I.V. hydration who were also recognized to have hyponatremia would be at risk for exacerbation of EAH from the I.V. hydration.

The hydration status of athletes presenting to the ED or hospital is unlikely to be evident unless the clinical assessment is clear for hypohydration from findings of orthostatic hypotension and persistent tachycardia (26,40,41). Otherwise, it has been demonstrated that the clinical assessment of hydration status in this population is unreliable (30,65,66). Hydration status may also be determined if body mass measurements have been made during the event and passed along to the ED, but accurate body mass assessment during endurance events is rare except when being performed for research purposes. Thus, the present work examined for distinguishing features within the typical laboratory data that might identify athletes at risk for exacerbation of EAH with aggressive hydration efforts among those presenting to the hospital with EAH and elevated serum creatinine or CK concentrations that could prompt concern over AKI. As anticipated, the present work demonstrates that there are no markers within the typical laboratory measures that will be clinically useful to differentiate this group.

It is fair to acknowledge that not all athletes with hypervolemic hyponatremia who receive aggressive I.V. hydration will develop symptomatic EAH or worsening of EAH symptoms. In the event that AVP suppression has occurred prior to I.V. hydration, it is possible that an aquaresis will prevent further lowering of serum sodium concentration during hydration, as seems evident through close scrutiny of case reports in which such treatment was used without inducing severe complications (30,67). Because AVP is not likely to be readily measured in the clinical setting, active urination may be a reliable sign to identify those with hypervolemic hyponatremia who are likely to not have an exacerbation of EAH with hydration efforts.

In this work, the conditions presumed to place an athlete at risk for receiving I.V. hydration if seen in the ED or hospital setting were a serum creatinine concentration meeting the AKI "risk" or worse criteria, or a serum CK concentration over 20,000 U/L. Such criteria are clearly far from adequately selective at identifying those who have a legitimate risk of AKI within this population of athletes, given that roughly two-thirds of the observations in this study met those criteria. Nevertheless, elevated serum creatinine concentrations and serum CK concentrations over 20,000 U/L are commonly used as criteria for aggressive hydration (20,23,56). It is also, unfortunately, rare for the medical literature to caution about EAH in describing the treatment for exercise-associated rhabdomyolysis (21,26,40,41).

Prior publications have discussed the excessive concern about dehydration, rhabdomyolysis, and the risk of developing AKI among endurance athletes (25,26,39–41). It is evident that body mass losses of 8% or more can occur among endurance athletes during events lasting up to 30 h without significant clinical symptomatology or adverse consequences (28,29). In fact, it should be quite rare for an ultramarathon runner to require postevent I.V. hydration. Such intervention should be limited to situations in which oral fluids are not tolerated and clear signs of hypovolemia are evident with persistent tachycardia, poor skin turgor, and lightheadedness with standing (26,40,41). Discriminate use of postevent I.V. hydration will obviously reduce the chance of exacerbating mild or asymptomatic EAH and the potentially serious consequences.

It is appropriate to comment on the cut-off that was used to characterize overhydration in this work. Overhydration was defined as no loss of body mass between measurements made at race registration and race finish (or last on-course body mass measurement in nonfinishers). Some body mass loss should be anticipated in a 161-km ultramarathon to maintain euhydration (61–63). On the other hand, we have previously found that body mass is typically a little higher immediately prerace compared with the prior morning (10). Among the present sample, body mass was measured within 1.5 h prior to the race start in 2011 and 2014, providing 388 pairs of body mass measurements for comparison. On average, body mass was 0.8% higher immediately prerace compared with the prior day. Thus, considering overhydration to be no loss of body mass based on measurement made the morning prior to the race start roughly means that a loss of ~1% body mass from immediately prerace was closer to the overhydration cut-off. Use of this cut-off may have still missed some runners who were slightly overhydrated at the finish, but it is unlikely to have incorrectly considered some runners to have been overhydrated when they were not, given the anticipated body mass loss required to maintain euhydration during a 161-km ultramarathon (62).

Limitations

The primary limitation of this work relates to the relatively small number of cases of postevent EAH in the present

sample. The incidence of EAH at the WSER has been relatively small in recent years after educational efforts about proper hydration (29). Such educational efforts have undoubtedly enhanced runner safety, but have come with inadvertent consequences to subsequent EAH-related research. One might also consider the lack of prerace serum creatinine concentration as a limitation, however, this would be typical of the situation of a postevent assessment in the ED or hospital setting. Finally, one could argue that it is questionable to consider those with mild biochemical EAH (values slightly below 135 mmol/L) and overhydration to be at risk for EAH exacerbation from aggressive hydration. This may have some merit because most symptomatic cases seem to have initial serum sodium concentrations below 130–132 mmol/L (28,31–37,42–47,49–51,67,68). However, symptomatic EAH has been reported with serum sodium concentrations as high as 133–134 mmol/L, so inclusion of those with mild biochemical EAH seems appropriate (28,42,45,49,68).

CONCLUSIONS

From this work, it can be concluded that the percentage of athletes at risk for exacerbation of asymptomatic or mildly symptomatic EAH from indiscriminate I.V. hydration of athletes after ultramarathons is small, though noteworthy. When an ultramarathon runner is known to have EAH and I.V. hydration is being considered for concern over rhabdomyolysis and AKI, there is a high likelihood that the athlete will have hypervolemic hyponatremia and be at risk for EAH exacerbation if treated with isotonic or hypotonic I.V. hydration. Among those most likely to receive aggressive I.V. hydration in an ED or hospital setting and with EAH, clinically distinguishing those with hypervolemic hyponatremia will be challenging. Thus, providers should use caution when hydrating any athlete after endurance events, particularly those with EAH, and recognize that very few will actually require I.V. hydration.

Acknowledgments—The author is grateful to the runners who have contributed to this work to advance knowledge. The author also thanks colleagues from previous publications from which the present data were attained and to those previously acknowledged in those publications. This material is the result of work supported with resources and the use of facilities at the VA Northern California Health Care System. The contents reported here do not represent the views of the Department of Veterans Affairs or the United States Government.

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ARTICLE SUMMARY

1. Why is this topic important?

Emergency physicians may have an inclination to treat athletes after endurance events with intravenous (I.V.) isotonic or hypotonic fluids due to concern about rhabdomyolysis and acute kidney injury, yet exercise-associated hyponatremia (EAH) is common after ultra-endurance events and the condition can be exacerbated by aggressive hydration. This work alerts emergency physicians about the associated risks of indiscriminate use of I.V. fluids in this population.

2. What does this study attempt to show?

This study predicts the percentage of athletes at risk for exacerbation of EAH from indiscriminate hydration after a 161-km ultramarathon in the field and hospital setting.

3. What are the key findings?

A small percentage (3%) of ultramarathon finishers were predicted to be at risk for exacerbation of EAH if aggressively hydrated after the ultramarathon. Based on serum creatine kinase and creatinine concentrations, it was estimated that two-thirds of the runners were at risk for receiving I.V. hydration if presenting to an emergency department, 8% of those had EAH, and nearly half (47%) of those at risk for receiving I.V. hydration and with EAH were also overhydrated, placing them at risk for EAH exacerbation. Among those at risk for receiving I.V. hydration and with EAH, there were no clinically useful laboratory findings to distinguish those at risk for EAH exacerbation with I.V. hydration.

4. How is patient care impacted?

Whether in the field or hospital setting, I.V. hydration of an athlete after an ultramarathon carries a notable risk for exacerbating EAH, so clinicians should use caution when hydrating athletes after endurance events.