

Exercise-Associated Hyponatremia and the Varon-Ayus Syndrome

Karina M. Soto-Ruiz, W. Frank Peacock

Abstract

Endurance sports such as marathon running are increasingly popular, attracting both professional and recreational athletes. While most participants recognize that these events can result in health hazards, few consider death a likely outcome. Exercise associated hyponatremia can be a consequence for which fatal outcomes may occur. In some it is mild and without symptoms. However,

in others it is of such severity that respiratory failure secondary to pulmonary edema, and possibly death may result. This article reviews new information regarding predisposing factors, treatment, and outcomes associated with exercise induced hyponatremia and the Varon-Ayus syndrome (hyponatremia, pulmonary edema and cerebral edema associated to marathon running).

Key words: Hyponatremia, non cardiogenic pulmonary edema, cerebral edema, marathon runners, endurance exercise, fluid overload, Varon-Ayus syndrome.

Introduction

Every year greater numbers of people participate in endurance sports, such as marathon running. From 2000 to 2007 the number of marathon finishers increased by 136%, from 299,000 to 407,000. (1) With this rate of increase many of today's competitors are not professional athletes, with a significant number being simply recreational runners. (2) As recently reported, it is the amateur athlete who represents the most vulnerable population for exercise induced health complications. (3)

Each year many marathon participants collapse, an event which identifies a cohort at risk for complications such as death. The true incidence of Exercise-Associated Hyponatremia (EAH) is not precisely known as many athletes with mild manifestations may not seek medical attention. Thus, the reported incidence of EAH is biased by recording only those with greater severity of illness and those who more often require medical attention. Overall, in patients seeking medical care, symptomatic hyponatremia is reported in 0.1 to 4% of athletes. (4) However, in a cohort of collapsed ultra-endurance athletes, the group with the greatest potential for severe illness, about 9% were found to have EAH. (4) In a separate study of 5082 participants in the 2002 Houston Marathon, the overall incidence of hyponatremia was 4.1 per 1000 participants, with 0.4 per 1000 developing severe hyponatremia. (5)

From School of Medicine, Universidad Autónoma de Baja California, Tijuana, México (Karina M. Soto-Ruiz) and Department of Emergency Medicine, The Cleveland Clinic, Cleveland, OH, USA (W. Frank Peacock).

Address for correspondence:

W. Frank Peacock
The Cleveland Clinic
9500 Euclid Ave, Cleveland, OH 44195, USA
Fax: +1 216-445-4552
E-mail: peacocw@ccf.org

Previous investigations into the possible etiologies resulting in marathon induced syncope identified fluid and electrolytes losses as the predominate cause of collapse. (6) While the underlying pathophysiology is unchanged since these

early publications, recommendations given to marathon participants have been significantly altered. Until the late 1960's, the standard fluid consumption recommendations were to restrict oral intake as it was believed it's ingestion impaired performance. (7,8) However, in 1969, reports emphasizing exercise induced dehydration hazards were published. (7) With a newer understanding of the performance implications and physiologic risks of excessive dehydration, fluid restriction recommendations were liberalized. By 1996, various athletic and medical societies published guidelines supporting large amounts of fluid intake. In fact, some encouraged athletes to 'drink as much as possible.' (7) These recommendations were based on the assumption that fluid loss during exercise should always be replaced, that the greatest health risk while exercising was dehydration, and that an excessive amount of fluid could do no harm. (8) This strategy was further supported by Kratz, et al, who published an analysis indicating that biochemical markers of dehydration were lessened by liberalized fluid intake during marathon running. (9)

Thus, as a result of the emphasis on increased volume intake, the prevalence of marathon induced dehydration diminished. While dehydration and its complications occurred much less frequently, the consequence of excessive hydration complicated by hyponatremia became an increasing medical problem. (8) A similar trend was noted in the United States military. Between 1989 and 1999, the US Army reported 190 cases of water intoxication requiring hospitalization, of which at least four died as a result of this condition. Ultimately, by 1999, the US military revised its fluid replacement guidelines. (10-13)

To protect runners from overhydration, the International Marathon Medical Directors Association (IMMDA) was created as the Consulting Medical Committee of the Association of International Marathons. This group represented medical experts in the field, as well as members from the USA Track and Field organization. Like the US military, in 2003 the IMMDA issued new fluid intake recommendations for marathon runners. They advised runners to drink *ad libitum* 400-800 ml/hr, with the higher rate for fast, heavier runners that compete in warm environments, and the lower rate for lighter slower runners. (2,13,14) While this recommendation was effective, cases of exercise induced hyponatremia continued to be

reported. Therefore in 2006 the IMMDA refined their recommendations. They suggested runners drink only to thirst, thus using thirst as a dynamic physiologic indicator of fluid requirements. In most cases, using thirst as a guideline, rather than a proscribed volume recommendation, protects the athlete from inadequate or excessive hydration by providing real time physiologic feedback. Concurrent with the newer recommendations, athletes were also advised to understand their individual fluid needs through the use of a static calculator but to defer to physiologic cues (i.e., thirst, weight gain, bloating, increased urination) when increasing or decreasing fluid intake. Finally, athletes were also instructed to consider environmental conditions, increasing fluid intake beyond thirst during the initial days of acclimatization in the setting of extreme heat, defined as exceeding 38 °C. (15)

Hyponatremia classification and the Varon-Ayus Syndrome

Exercise associated hyponatremia (EAH) is defined as plasma sodium levels below the reference range of the laboratory performing the test, usually less than 135 mmol/L (9) that presents within 24 hours after prolonged physical activity. (16) EAH is dichotomized into asymptomatic and symptomatic cohorts. When no symptoms are reported by the athlete, or when they are so mild that the athlete does not seek medical attention, it is classified as asymptomatic hyponatremia. (17) Symptomatic hyponatremia manifests a broad spectrum of complaints ranging from malaise, nausea, fatigue, lightheadedness, and headache, to confusion, seizures, coma and death. (18) It has been observed that the severity of symptoms correlates with the serum sodium concentration. (19) When serum sodium concentration falls below 125 mmol/L, athletes are more likely to be symptomatic, while the majority of athletes with a serum sodium concentration between 130 and 134 mmol/L are asymptomatic. (19)

Marathon induced hyponatremia can present with severe life threatening end organ damage. In 2000, Ayus, Varon and Arieff reported a series of seven runners that developed life threatening hyponatremia after marathon completion. All were admitted to the hospital with nausea, emesis, pink

frothy sputum, and pulmonary edema. Echocardiograms revealed each had a normal ejection fraction, suggesting a cardiac etiology was not the cause. All patients required mechanical ventilation due to hypoxemic respiratory failure. Computed tomography or magnetic resonance imaging of the brain performed in six of the patients revealed cerebral edema. In the one patient in who brain imaging was not done, hyponatremic encephalopathy was not suspected. This patient subsequently suffered a cardiopulmonary arrest, died, and was found to have pulmonary edema and cerebral edema with brainstem herniation at autopsy. Six of the patients were treated with intravenous NaCl and plasma sodium levels increased by 10 mmol/L in less than 12 hours. It was observed that as plasma sodium levels increased, the cerebral and pulmonary edema resolved, and all patients recovered. This condition was later described as the Varon-Ayus Syndrome (VAS). (20)

Mechanisms of pathogenesis

The etiology of EAH and VAS is not entirely known, although many theories have been proposed. Hiller, et al, during the Hawaiian Ironman triathlon, observed that 70% of the athletes treated for hyponatremia were also considered to be dehydrated; therefore they concluded that EAH was due to salt depletion and dehydration. This theory was not widely accepted as it was based solely on observational assessments and no supporting evidence was provided. Another theory suggested volume overload as the cause of exercise associated hyponatremia, as evidence suggested a correlation between fluid intake and decreased plasma sodium values. (21) This is one of the most widely accepted theories as authors have found a correlation between weight gain during exercise and the subsequent exercise associated hyponatremia. While weight gain may be a risk factor for EAH, it is not the sole explanation as it has also been observed that some athletes who gain weight during exercise do not develop hyponatremia. (22)

Another proposed EAH mechanism is based upon the inadequate secretion of arginine vasopressin (AVP). In some hyponatremic athletes, AVP serum levels measured after exercise were found to be within normal range. Normal post-exercise AVP levels would not be expected to

be present as the AVP concentration should be low in the setting of serum hypoosmolality. This suggests an exercise induced syndrome of inappropriate of antidiuretic hormone (SIADH). (23) SIADH as the etiology of EAH is further supported by the fact that an elevated urine osmolality has also been found in some athletes. (22) Siegel, et al have postulated that skeletal muscle cells injured during exercise, with a subsequent release of inflammatory cytokines such as interleukin 6 (IL-6), may play a role in AVP secretion. (22) Mastorakos, et al have demonstrated that IL-6 can act as an AVP secretagogue, and it has also been shown in rat models that IL-6 reduces the expression of aquaporin-2, an AVP target and diuresis regulator. (22)

Risk factors

In 2005, the first International Exercise-Associated Hyponatremia Consensus Development Conference was created to review existing data on EAH. Their objectives were to create an integrated analysis synthesizing data on the latest in incidence, prevalence, etiology and treatment of EAH, and make it available to physicians and public in general. The second consensus, held in 2007, identified numerous risk factors and classified EAH into event or athlete related. Event related risk factors include events lasting more than 4 hours, high or extremely cold temperatures, and a high availability of drinking fluids. Athlete related risk factors, listed in **Table 1**, constitute those characteristics where education would be expected to have the greatest impact on the frequency of EAH.

Underlying medical risk factors may also contribute to the risk of EAH. These include predisposing conditions such as SIADH, intrinsic renal disease resulting in alteration of the kidney to excrete water, or the concurrent use of drugs such as selective serotonin re-uptake inhibitors or thiazide diuretics. The increased risk of EAH in women was thought to be related to the fact that women marathon participants may have a lower BMI than their male counterpart. However, it has recently been suggested gender differences may be the consequence that women have higher levels of IL-6 during exercise induced stress than do men. Finally, there is also data suggesting that estrogens decrease the stimulation to consume sodium when salt deprived. (24,25)

Management

The treatment of EAH and VAS is dictated by the severity of the presentation. When a patient has asymptomatic hyponatremia, no treatment beyond observation and supportive care is indicated. (17) Asymptomatic hyponatremia is usually detected when electrolytes are measured for other reasons. In this setting it is recommended that athletes restrict their fluid intake until urination is present. (16)

For patients with symptomatic hyponatremia, but who do not have signs or symptoms of pulmonary or cerebral edema, management is focused on serum sodium monitoring and observation. Intravenous fluids (IVF) are not generally indicated as fluid overload is usually present. (17)

Severe hyponatremia may present with altered mental status, vomiting, seizures, or respiratory insufficiency. When neurologic findings are consistent with encephalopathy, administration of 3% hypertonic saline is recommended. To acutely diminish cerebral edema, an initial 100 ml bolus of 3% NaCl has been shown to increase serum sodium concentration 2 to 3 mmol/L. The initial bolus can then be repeated by two additional boluses at 10 minutes intervals. With these therapeutic measures no cases of osmotic demyelination or central pontine myelinolysis have been reported. (16)

Patients with symptomatic hyponatremia should be emergently transferred to a medical facility with ICU capability for close monitoring and to continue hypertonic saline administration. It is recommended to give 3% hypertonic saline at a rate of 1 to 2 ml/kg per hour while closely monitoring serum and urinary electrolytes. The rate of administration can be increased to 3 to 4 ml/kg per hour if the patient does not respond to the initial treatment. Consideration for stopping the hypertonic saline infusion may occur once diuresis begins.

When patients present with hyponatremic pulmonary edema, this same 3% saline replacement schedule may be considered as outcome is greatly improved when rapid sodium replacement is performed. As the administration of a loop diuretic results in the production of dilute urine, in the setting of severe volume overload, its concurrent usage may also be considered.

More recently, the use of vasopressin receptor antagonists

(VRA) such as lixivaptan, tolvaptan and conivaptan has been suggested. While these agents have been successfully used to treat hyponatremia associated with cirrhosis, congestive heart failure, and SIADH, their use in EAH and VAS remains controversial due to the theoretical risk that athletes might develop hypernatremia secondary to an extremely rapid water diuresis. Furthermore, it is unknown if VRA's should be used alone or in conjunction with hypertonic saline. Thus, until further studies are completed, they are not currently recommended for treating EAH.

Prevention

As with any pathologic event, prevention represents the optimal strategy to avoid adverse outcomes. As participant education represents an important tool in the prevention of EAH, the International Marathon Medical Directors Association (IMMDA) has recommended that information regarding the signs and symptoms of EAH be available to all runners at the time of registration for a competition. (26)

In addition to replacing volume based on thirst, as recommend by the 2007 International Consensus of Exercise Associated Hyponatremia, runners are also advised to know their personal fluid requirements. Knowledge of an individual's personal fluid requirements is obtained by weighing themselves while training to determine the amount of fluid they may ingest without gaining weight. (15)

Knowledge of baseline weight at the start of the competition is also recommended. As EAH should be considered in the differential diagnosis of any athlete who presents for medical attention and has maintained or gained weight during a competition, multiple authors support having all runners weighed before a race begins. This information should then be available for medical personnel (26) as it is expected for a runner to lose 2% of the initial body weight during a marathon.

Finally, the IMMDA does not recommend the use of any proprietary sport drinks or salt tablet supplementation. The lack of support for sport drinks is because most are hypotonic and their use could result in dilution of sodium if excess water retention occurred during exercise. (16) Lastly, there was no clear support for prophylactic oral sodium

supplementation in either liquid or tablet form, as they have not been shown to reduce the incidence of EAH. (16)

Conclusions

EAH and the VAS should be considered in the setting of endurance exercise. Clinicians should know the signs of symptoms of hyponatremia and have the necessary equipment available to make a diagnosis. If not possible within the ambulatory setting, appropriate patients should be treated based on clinical suspicion and transferred for higher level of care. If neither identified nor treated, EAH and the VAS may have potentially fatal complications. Further studies are needed to

entirely understand the mechanism of EAH and to increase the safety margin of participation in these types of sporting events.

Table 1. Athlete Related Risk Factors for Exercise-Associated Hyponatremia.

- 1) Excessive drinking behavior (regardless of fluid type)
- 2) Low body weight (defined as a body mass index equal or below 20)
- 3) Slow running pace (slower athletes have more opportunities to drink)
- 4) Non-steroidal anti-inflammatory drug use
- 5) Weight gain during exercise
- 6) Event inexperience
- 7) Female sex
- 8) Underlying medical condition

References

1. MarathonGuide.com Staff. USA Marathoning: 2007 Overview [Online]. 2007 [cited 2009 June 28]; Available from: URL:<http://www.marathonguide.com/features/Articles/2007RecapOverview.cfm>.
2. Noakes T, IMMIDA. Fluid replacement during marathon running. *Clin J Sport Med* 2003;13:309-18.
3. Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005;352:1550-6.
4. Noakes TD, Norman RJ, Buck RH, Godlonton J, Stevenson K, Pittaway D. The incidence of hyponatremia during prolonged ultraendurance exercise. *Med Sci Sports Exerc* 1990;22:165-70.
5. Carter R. Exertional heat illness and hyponatremia: an epidemiological prospective. *Curr Sports Med Rep* 2008;4:20-27.
6. Hsieh M, Roth R, Davis DL, Larrabee H, Cllaway CW. Hyponatremia in runners requiring on-site medical treatment at a single marathon. *Med Sci Sports Exerc* 2002;34:185-9.
7. Kratz A, Siegel AJ, Verbalis JG, Adner MM, Shirey T, Lee-Lewandrowski E, et al. Sodium status of collapsed marathon runners. *Arch Pathol Lab Med* 2005;129:227-30.
8. Noakes TD. Overconsumption of fluids by athletes. *BMJ* 2003;327:113-4.
9. Kratz A, Lewandrowski KB, Siegel AJ, Chun KY, Flood JG, Van Cott EM, et al. Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers. *Am J Clin Pathol* 2002;118:856-63.
10. Garigan TP, Ristedt DE. Death from hyponatremia as a result of acute water intoxication in an Army basic trainee. *Mil Med* 1999;164:234-8.
11. Montain SJ, Sawka MN, Wenger CB. Hyponatremia associated with exercise: risk factors and pathogenesis. *Exerc Sports Sci Rev* 2001;29:113-7.
12. Montain SJ, Latzka WA, Sawka MN. Fluid replacement recommendations for training in hot weather. *Mil Med* 1999;164:502-8.
13. O'Brein KK, Montain SJ, Corr WP, Sawka MN, Knapik JJ, Craig SC. Hyponatremia associated with overhydration in U.S. Army trainees. *Mil Med* 2001;166:405-10.
14. Kolka MA, Latzka WA, Montain SJ, Corr WP, O'Brien KK, Sawka MN. Effectiveness of revised fluid replacement guidelines for military training in hot weather. *Aviat Space Environ Med* 2003;74:242-6.
15. Hew-Butler T, Verbalis JG, Noakes TD; International Marathon Medical Directors Association. Updated fluid recommendation: position statement from the International Marathon Medical Directors Association (IMMDA). *Clin J Sport Med* 2006;16:283-92.
16. Hew-Butler T, Ayus JC, Kipps C, Maughan RJ, Mettler S, Meeuwisse WH, et al. Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. *Clin J Sport Med* 2008;18:111-21.
17. Speedy DB, Noakes TD, Schneider C. Exercise-associated hyponatremia: a review. *Emerg Med (Fremantle)* 2001;13:17-27.
18. Wolfson AB. Acute hyponatremia in ultra-endurance athletes. *Am J Emerg Med* 1995;13:116-7.
19. Speedy DB, Noakes TD, Rogers IR, Thompson JM, Campbell RG, Kuttner JA, et al. Hyponatremia in ultradistance triathletes. *Med Sci Sports Exerc* 1999;31:809-15.
20. Ayus JC, Varon J, Arieff AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med* 2000;132:711-4.
21. Reid SA, Speedy DB, Thompson JM, Noakes TD, Mulligan G, Page T, et al. Study of hematological and biochemical parameters in runners completing a standard marathon. *Clin J Sport Med* 2004;14:344-53.
22. Rosner MH, Kirven J. Exercise-associated hyponatremia. *Clin J Am Soc Nephrol* 2007;2:151-61.
23. Siegel AJ, Verbalis JG, Clement S, Mendelson JH, Mello NK, Adner M, et al. Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. *Am J Med* 2007;120:461.e11-7.
24. Stricker EM, Thiels E, Verbalis JG. Sodium appetite in rats after prolonged dietary sodium deprivation: a sexually dimorphic phenomenon. *Am J Physiol* 1991;260:R1082-8.
25. Barron WM, Schreiber J, Lindheimer MD. Effect of ovarian sex steroids on osmoregulation and vasopressin secretion in the rat. *Am J Physiol* 1986;250:E352-61.
26. Chorley JN. Hyponatremia: identification and evaluation in the marathon medical area. *Sports Med* 2007;37:451-4.