Exercise-Associated Hyponatremia

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Exercise-associated hyponatremia has been described after sustained physical exertion during marathons, triathlons, and other endurance athletic events. As these events have become more popular, the incidence of serious hyponatremia has increased and associated fatalities have occurred. The pathogenesis of this condition remains incompletely understood but largely depends on excessive water intake. Furthermore, hormonal (especially abnormalities in arginine vasopressin secretion) and renal abnormalities in water handling that predispose individuals to the development of severe, life-threatening hyponatremia may be present. This review focuses on the epidemiology, pathogenesis, and therapy of exercise-associated hyponatremia.

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Severe and potentially life-threatening hyponatremia can occur during exercise, particularly in athletes who participate in endurance events such as marathons (42.2 km), triathlons (3.8 km of swim, 180 km of cycling, and 42.2 km of running), and ultradistance (100 km) races. In fact, hyponatremia has been stated to be one of the most common medical complications of long-distance racing and is an important cause of race-related fatalities (1). On the basis of recent studies of the incidence and risk factors of hyponatremia in endurance athletes, along with well-publicized reports of fatalities as a result of hyponatremia, medical directors and marathon organizations have begun to warn participants of the dangers of hyponatremia and excessive fluid intake (2).

Exercise-associated hyponatremia (EAH) first was described in Durban, South Africa, in 1981; subsequently, Noakes *et al.* (3) in 1985 described the occurrence of severe hyponatremia in four athletes who participated in endurance events that were longer than 7 h. This report was followed by a similar paper by Frizzel *et al.* (4) that described the development of EAH in two of the authors. Importantly, before 1981, athletes were advised to avoid drinking during exercise, leading to the development of hypernatremia and dehydration in some athletes (5). Since that time, it generally has been advised that athletes consume as much fluid as possible during exercise, and rates of fluid intake during running races vary widely from 400 to 1500 ml/h or greater (6–8). In fact, most race organizers currently provide copious supplies of water and "sports beverages" throughout the race course to fend off dehydration. Concomitant with these recommendations, the incidence of hyponatremia in athletes seems to be increasing, especially in the United States (1,9–13). As the popularity of marathon races and other endurance events increase, more athletes are likely to be at risk for the development of EAH.

EAH can take two forms, depending on whether specific symptoms that are attributable to hyponatremia are present (14). Athletes may present with symptoms such as confusion, seizures, and altered mental status in association with serum sodium levels <135 mmol/L and are considered to have exercise-associated hyponatremic encephalopathy (EAHE). Alternatively, athletes may present with isolated serum sodium levels <135 mmol/L without easily discernible symptoms and have EAH.

This review focuses on important historic, epidemiologic, and pathophysiologic aspects of this condition, highlighting recent articles that show the importance of excessive water intake in the genesis of EAH. Important treatment-related issues also are discussed.

Incidence

Until recently, the incidence of hyponatremia during endurance exercise was unknown and thought to be relatively uncommon. However, recent studies have shown that endurance athletes not uncommonly develop hyponatremia at the end of the race, usually in the absence of clear central nervous system symptoms (9,10,12,15–25). For example, in the 2002 Boston Marathon, Almond *et al.* (15) found that 13% of 488 runners studied had hyponatremia (defined as a serum sodium concentration of 135 mmol/L or less) and 0.6% had critical hyponatremia (serum sodium concentration of 120 mmol/L or less). Speedy *et al.* (21) investigated 330 athletes who finished an ultramarathon race. In this study, 58 (18%) were hyponatremic (defined as a serum sodium <135 mmol/L) and 11 had severe hyponatremia (serum sodium <130 mmol/L). Studies of other endurance events have reported the incidence of hyponatremia to be up to 29% (9,10,12,15–25). These incidence rates may be overestimations as a result of sampling biases. For example, in the 2002 Boston Marathon study, of 766 runners enrolled in the study, only 488 runners had serum sodium values assayed (15). Some of these runners did not finish the race, and others had

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time constraints that did not allow them to have blood samples obtained. As is discussed later, the majority of these athletes are asymptomatic or mildly symptomatic (nausea, lethargy). However, severe manifestations such as cerebral edema, noncardiogenic pulmonary edema, and death can occur (11–14).

There have been at least 8 reported deaths from EAH (5,10,11,26–29). Many of these reports relate to a series of fatalities in the military between 1989 and 1996 (27–29). During this period, military recruits were encouraged to ingest 1.8 L of fluid for every hour they were exposed to temperatures above 30°C (30). At least four other deaths have been attributed to EAH in the United States (5,10,11,26,31). It is interesting that two of these deaths occurred in doctors (31). The exact incidence of mortality related to EAH is not known but is likely to be low.

Risk Factors

Several risk factors have been linked with the development of EAH (Table 1). The major risk factor seems to be overhydration or excessive fluid consumption during activity (reviewed in reference [31]). This first was suggested by Noakes *et al.* in their original publication in 1985 and confirmed in this group's later studies (3,5,21). The chronological history of the incidence of EAH also points to the primary role of overhydration in the pathogenesis. Before 1981, athletes were encouraged to drink heavily during exertion to avoid dehydration (7,31). With the description of EAH in South Africa and New Zealand in 1985, new fluid consumption guidelines that restricted overzealous fluid intake for endurance events in these countries were promoted (32,33). Concomitant with these recommendations, the incidence of EAH fell in both of these regions (19,20). Similar observations were made after the US military revised its guidelines for fluid consumption during training activities after the incidence of EAH increased (31). With an upper limit of fluid consumption set at 1.0 to 1.5 L/h, the incidence of EAH in the US military fell (31).

In a study of runners in the Boston Marathon, Almond *et al.* (15) found significant correlations between fluid intake and the incidence of hyponatremia. Specifically, a fluid intake of >3 L, a postrace weight greater than prerace weight, self-reported water loading (increased fluid consumption above baseline in preparation for the marathon), and self-reported fluid intake during the race all were found to be significant predictors for the development of hyponatremia ($P < 0.05$) (15). Substantial weight gain during the duration of the activity seemed to be the most important predictor of hyponatremia and correlated well with increased fluid intake. Speedy *et al.* (21) also found correlations between intrarace weight gain and hyponatremia; 73% of patients who were found to be severely hyponatremic had either gained or maintained weight during the race. Noakes *et al.* (34) in the largest study to date investigated the changes in serum sodium concentration associated with changes in body weight in 2135 endurance athletes. The mean ± SD serum sodium was 136.1 ± 6.4 mmol/L for athletes who gained weight during the race, 140.5 ± 3/7 mmol/L for those with minimal weight gain, and 141.1 ± 3.7 mmol/L for those who lost weight during the race. The authors estimated that athletes who gained >4% body weight during exercise had a 45% probability of developing hyponatremia. Importantly, 70% of individuals who gained weight during exercise did not develop hyponatremia, pointing to other important factors in the pathogenesis, as discussed next (34).

Table 1. Risk factors for the development of EAH[a]

Exercise duration >4 h or slow running/exercise pace
Female gender (may be explained by lower body weight)
Low body weight
Excessive drinking (>1.5 L/h) during the event
Pre-exercise overhydration
Abundant availability of drinking fluids at the event
Nonsteroidal anti-inflammatory drugs (not all studies)
Extreme hot or cold environment

[a]EAH, exercise-associated hyponatremia.

Almond *et al.* (15) were not able to find a correlation in the type of fluids consumed (water *versus* electrolyte-containing solutions) and the subsequent development of hyponatremia. Other studies also have shown that the consumption of a carbohydrate/electrolyte-containing sports drink does not protect against the development of hyponatremia (35–38). This likely reflects the relative hypotonicity of most of the commercial sports drinks in which the sodium concentration typically is 18 mmol/L (39).

Gender likely plays a role in the risk for development of EAH, with female athletes more likely than male athletes to develop hyponatremia during endurance events (10–12,15,21,40). Of 26 cases of EAH reported after the San Diego Marathon, 23 occurred in women (12). Hyponatremia was three times more common in women than in men in the 1997 New Zealand Ironman triathlon (21). Almond *et al.* (15) also found that hyponatremia developed more commonly in women in the Boston Marathon. However, in this study, when these results were corrected for body mass index, racing time, and weight change, the difference did not reach statistical significance, suggesting that body size and duration of exercise may explain the gender differences. Furthermore, the incidence of hyponatremia in US military recruits reflects the gender distribution of this cohort and is not skewed to women (41). Some investigators also have suggested that women adhere more stringently to hydration recommendations during exercise and therefore consume more fluids (42). The finding of a gender association for the risk for symptomatic hyponatremia also has been seen in the postoperative state. Ayus *et al.* (43) noted that despite equal incidences of postoperative hyponatremia in men and women, 97% of those with permanent brain damage were women and 75% of them were menstruant. This predisposition likely is explained by the effects of sex hormones on the Na^+-K^+-ATPase (44). Both estrogen and progesterone inhibit the function of the Na^+-K^+-ATPase, which normally has an important function in the extrusion of sodium from cells during the development of hyponatremia. Ultimately, this inhibition may result in a higher risk for cerebral edema and increased intracranial pressure in women who are exposed to acute hyponatremia.

The development of hyponatremia also has been correlated with the number of marathons run, the training pace, and the race duration (10,12,15,45). Those who have run fewer marathons (less experienced runners), have slower training paces, and have longer race times (especially >4 h) each were shown independently to have a significantly higher risk for developing hyponatremia (10,12,15,45). Longer race times likely correlate with increased water consumption and increased sodium losses (10,12,46). For example, participants who developed hyponatremia in the 1998 and 1999 San Diego Marathons had an average finishing time of 5 h and 38 min, and many of these individuals admitted to drinking as much fluid as possible during and after the event (12). A low body mass index also was shown to be a significant risk factor, perhaps as a result of the ingestion of larger amounts of fluid in proportion to size and total body water (TBW) (15).

Medications also may play a significant role in the hyponatremia that is found in endurance athletes, but this largely is unproved. Nonsteroidal anti-inflammatory drug (NSAID) use is common among marathon runners, being used in 50 to 60% of men and women, respectively (10,22,47). NSAID are known to potentiate the effects of arginine vasopressin (AVP) by inhibiting renal prostaglandin synthesis *via* the COX-2 isoform of cyclo-oxygenase (48–50). Furthermore, NSAID decrease the GFR when given to those with effective volume depletion, such as exercising endurance athletes (51). These effects may impair the urine-diluting capacity of the kidney (51). Despite these theoretical considerations, Almond *et al.* (15) were unable to associate the use of NSAID with the development of hyponatremia in the runners who were studied in the 2002 Boston Marathon. Other studies also have not been able to ascribe conclusively to NSAID use the development of hyponatremia, although several of these studies were underpowered to do so (10,22). However, a recent study in 330 triathletes demonstrated a significant association of NSAID use and the development of hyponatremia (23). In this study, the incidence of NSAID use in athletes was 30%, and NSAID use was highly associated with the development of hyponatremia ($P = 0.0002$), as well as higher plasma potassium and creatinine levels. Several other, smaller studies and case reports also have suggested a potentiating role for NSAID use (11,12,52). Therefore, the role of NSAID in the development of EAH remains controversial but in some runners likely is a potentiating factor. Whether other medications, such as selective serotonin reuptake inhibitors or thiazide diuretics, that are associated with hyponatremia in nonathletes can potentiate the development of EAH is not known. It is important to recognize that these risk factors do not suggest causation or even an independent association with the development of hyponatremia. However, they do offer important clues to the pathogenesis of the condition.

Pathophysiology

Normally, renal and hormonal systems maintain the plasma osmolality within tight limits with variability of no more than 1 to 2% (reviewed in reference [53]). These tight limits reflect the physiologic importance of osmolality regulation on cell volume and function (54). The development of hyponatremia (usually, in the setting of hypo-osmolality) reflects either defects in these hormonal and renal control mechanisms or water ingestion that overwhelms them. In the specific instance of EAH, defects in renal diluting mechanisms, hormonal control of water excretion, excessive sodium losses, and excessive water intake all contribute to the development of hypo-osmolality (summarized in Figure 1).

Current evidence strongly supports that EAH is, in large part, dilutional in nature. In the majority of athletes who develop hyponatremia, there is an increase in TBW relative to that of total body exchangeable sodium (34). As described previously, this seems to occur by the ingestion of hypotonic fluids (water or sports drinks) in excess of sweat, urine, and insensible (mainly respiratory and gastrointestinal) losses. In a seminal study, Noakes *et al.* (34) described a linear relationship with a negative slope between the serum sodium after racing and the degree of weight change in 2135 athletes (Figure 2). The primary cause of this weight gain during exercise must be the consumption of fluids during exercise. This consumption of fluids during exercise can be driven by thirst or through conditioned behavior. Some have hypothesized that in some athletes, the thirst drive may be excessive, but, more likely, the excessive fluid intake during exercise reflects conditioned behavior that is based on recommendations to drink fluid during exercise to avoid dehydration as well as the wide availability of fluids along the race course (31,55). This hypothesis is supported by data, previously described, that the incidence of EAH was rare or nonexistent before 1981, when recommendations for fluid intake during exercise were conservative. EAH was seen only after recommendations for more aggressive hydration were promulgated (31). Occasionally, some athletes may drink up to 3 L/h in an attempt to produce dilute urine to escape detection of banned drugs in the urine (56). Finally, some athletes may drink large volumes of fluid in the days leading up to a marathon in an attempt to ward off dehydra-

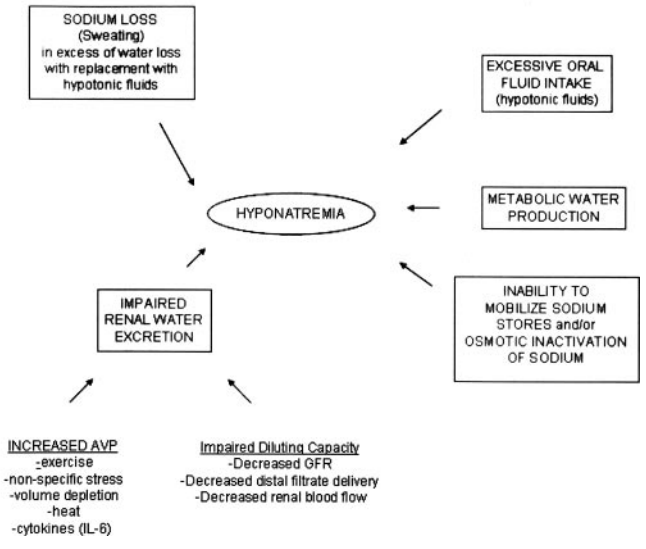

Figure 1. Pathophysiologic factors in the development of exercise-associated hyponatremia (EAH). AVP, arginine vasopressin.

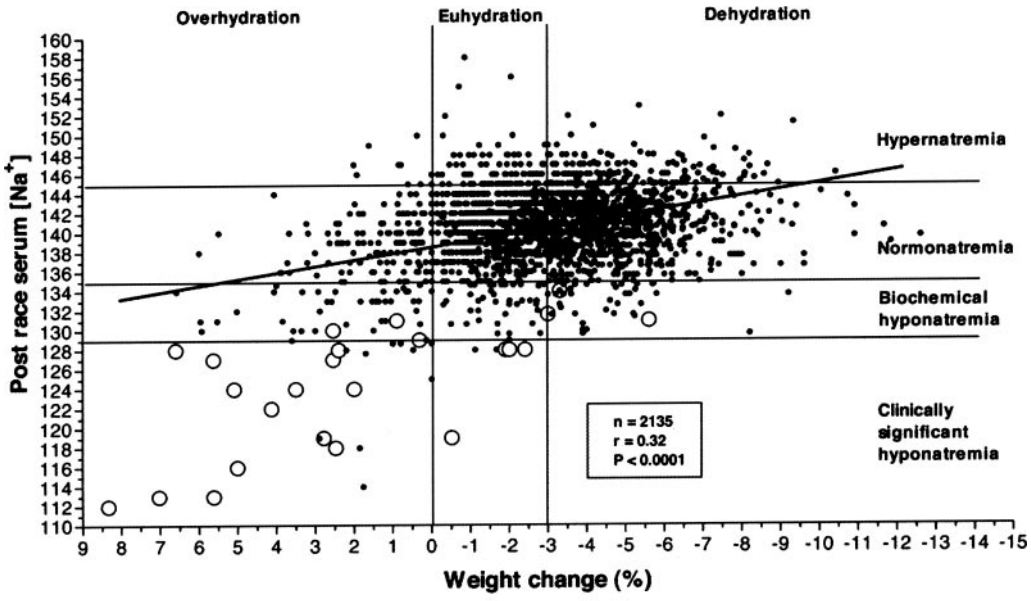

Figure 2. Relationship between serum sodium after racing and the weight change (in %) during exercise in 2135 athletes who competed in endurance events. ●, asymptomatic athletes; ○, athletes with symptoms compatible with EAH encephalopathy (EAHE). The majority of athletes who develop clinically significant hyponatremia have positive weight changes. Reprinted from reference (34), with permission. Copyright 2005 National Academy of Sciences.

tion. This was the case for one female runner who drank 10 L of fluid on the evening before a marathon and then experienced postrace hyponatremia (57).

However, excessive fluid consumption is not the sole explanation for the development of EAH. In the study of Noakes *et al.* (34), hyponatremia did not develop in 70% of the athletes who overconsumed fluids and had an increase in TBW. This indicates that other important factors must be operational in the pathogenesis of EAH. The importance of other factors also is highlighted by the fact that the maximum water excretory capacity of the kidneys is between 750 and 1500 ml/h (53). In combination with fluid losses from sweating and insensible losses (which may be in excess of 500 ml/h), most athletes should be able to consume fluids in excess of 1500 ml/h before retaining weight and increasing TBW. This amount of fluid consumption is at the upper limit of what most athletes would consume during an activity (31). Therefore, either defects in renal water excretion and/or significant sodium losses or failure to mobilize exchangeable sodium stores may occur in athletes who develop EAH. Furthermore, some athletes develop hyponatremia without appreciable gains in total body weight (34). As discussed next, these athletes may have significant sodium losses or also may have gained net body free water as a result of the metabolism of glycogen and triglycerides and not as a result of ingestion. However, the contribution of fuel metabolism or metabolic water production to TBW likely is small. During treadmill running at 74% of maximal oxygen consumption, metabolic water production averages 144 g/h (in contrast, sweat loss during this time was 1200 g/h) (58). There is a possibility that water that is stored with glycogen can be released with glycogen breakdown. This may be an important component in the cause of hyponatremia that occurs without weight gain because each kilogram of glycogen can contain upwards of 3 kg of associated water (59,60).

Data on the levels of AVP during exercise are conflicting. Unfortunately, systematic measurement of AVP levels or free water clearances in athletes who present with hyponatremia has not been done except in isolated cases. There are several potential pathways for stimulation of AVP release in exercising athletes. Controlled laboratory studies have demonstrated that as exercise intensity increases above 60% of maximal oxygen consumption, there are concomitant increases in AVP levels (61). Nonspecific stresses that are experienced by athletes and caused by factors such as pain, emotion, or physical exercise have been thought to cause nonosmotic release of AVP (62). However, it is difficult to determine whether this effect is mediated by a specific pathway or is due to a secondary stimulus, such as hypotension or nausea, that may occur in exercising athletes. AVP production also may be stimulated appropriately in athletes who develop volume depletion. However, the level of volume depletion that is required to stimulate AVP production in the absence of hyperosmolality is in excess of 7 to 8% of body volume. These levels of volume depletion typically are not seen in athletes (*e.g.*, in the 2001 South African Ironman Triathlon, only 7% of finishers had a net body weight loss >5% [20]). Furthermore, the majority of athletes with EAH finish events with an increase in body weight and possibly an expanded plasma volume (34). Exposure to heat also can lead to the secretion of AVP (63). However, this effect of temperature may be influenced secondarily by changes in effective arterial volume that occur with heat-induced vasodilation. Despite these considerations, in some athletes during prolonged exer-

cise, plasma AVP levels may not be suppressed maximally despite maintenance or even excess of plasma volume. This has been described in studies of hikers who developed hyponatremia in the Grand Canyon and in an army recruit during a prolonged field march (40,64). Speedy *et al.* (46) also described median AVP levels that were significantly higher in athletes who developed hyponatremia in the 1997 New Zealand Ironman Triathlon.

An intriguing link between exercise and the nonosmotic stimulation of AVP release may be related to the release of inflammatory cytokines by the exercising and injured skeletal muscle as postulated by Siegel (65). As glycogen stores are depleted, rhabdomyolysis or lesser degrees of muscle injury can occur with the release of inflammatory cytokines such as IL-6. Independent of rhabdomyolysis, studies have shown that exercise primes an array of pro- and anti-inflammatory and growth factor expressions within circulating leukocytes (66,67). Mastorakos *et al.* (68) demonstrated that IL-6 can act as an AVP secretagogue. This effect of IL-6 on hypothalamic AVP secretion also was seen in children after head trauma (69). It is interesting that women respond to exercise-induced stress with the production of higher levels of IL-6, perhaps explaining, in part, the increased risk for EAH in women (66). Along these lines, single-nucleotide polymorphisms in the promoter region of inflammatory cytokines are important in determining the levels of cytokine production (70). A particular athlete may be predisposed to EAH on the basis of the single-nucleotide polymorphism profile and specific inflammatory response to exercise. Conversely, IL-6 in a rat sepsis model has been shown to reduce the expression of aquaporin-2, the downstream target of AVP and ultimate regulator of water diuresis (71). How these factors interact to cause EAH is not known but should be an avenue of research.

Consistent with the probable role of AVP in EAH, athletes who have finished races with hyponatremia have also been demonstrated, in some cases, to have inappropriately elevated urine osmolality (72). In this setting, even small increases in plasma AVP levels can cause significant water retention and hyponatremia, especially in combination with excessive water intake. Furthermore, gastrointestinal blood flow and water absorption from the stomach and intestine may be impaired during exercise (73). When the athlete stops activity, water absorption may increase rapidly and significantly (73). In the setting of elevated AVP levels, this rapid absorption of large quantities of water or hypotonic fluids can lead to significant falls in serum sodium.

Whether AVP levels are increased inappropriately in all athletes who develop EAH is not known. Speedy *et al.* (74) measured normal (suppressed) AVP levels in two triathletes who developed hyponatremia during an Ironman event and demonstrated that other causes for renal impairment of free water excess must be present in some athletes. A possible cause of EAH is that during exercise, the diluting capability of the kidney is likely to be diminished (75). In both the thick ascending limb of Henle and the distal tubule, reabsorption of sodium chloride in the absence of water (and thus dilution of the urine) depends on the delivery of filtrate to these segments and is affected by the renin-angiotensin-aldosterone system, the sympathetic nervous system, renal blood flow, and proximal tubular reabsorption of sodium. During exercise, there is a release of catecholamines and angiotensin II that leads to an increase in sodium and water reabsorption in the proximal tubule, thereby decreasing the amount of filtrate that is delivered to the distal diluting segments of the kidney (75). Furthermore, renal blood flow and GFR are decreased in the setting of endurance exercise and further limit the delivery of filtrate to the diluting segments of the kidney (75). These effects on the diluting capacity of the kidney may be significant in leading to impairments of free water excretion.

Although overdrinking clearly is the most important causative factor in the development of EAH, there is a variable and important contribution of sodium loss from sweating (38). The concentration of sodium in sweat varies widely but is usually 15 to 65 mEq/L, with highly fit athletes generally excreting sweat with sodium concentrations <40 mEq/L (38,76). The volume of sweat during exercise also varies widely, from approximately 250 ml/h to >2 L/h, again being less in more fit athletes (77,78). This loss of a substantial amount of hypotonic fluid may seem to protect against the development of hyponatremia. However, these losses are replaced by the ingestion of more hypotonic fluids (water or sports drinks), and the extracellular volume loss in sweat may serve as a stimulus for antidiuretic hormone (ADH) secretion. In fact, mathematical models demonstrate that the magnitude of sweat sodium loss is insufficient to produce EAH (38,79). For example (as discussed in reference [38]), in a 90-km ultramarathon race, an athlete may lose approximately 8.6 L of sweat. Assuming sweat sodium concentrations of either 25 or 50 mmol/L and that all fluid losses were replaced by water, the resulting sodium deficits would be 215 and 430 mmol, respectively. For a 70-kg athlete, the resulting serum sodium concentration would be either 135 or 130 mmol/L, respectively. However, for longer duration events and for those with high sweat sodium concentrations (>75 mmol/L), a sufficient sweat sodium deficit can occur for athletes to finish the race both dehydrated and hyponatremic. This is supported by the finding that some athletes finish races with net weight loss and hyponatremia (34). Furthermore, one case report of a patient who had cystic fibrosis (patients with cystic fibrosis excrete large amounts of sodium in their sweat) and developed EAH points to the possibility that some people may be genetically predisposed to EAH as a result of high sweat sodium losses (80).

As mentioned previously, in the study by Noakes *et al.* (34) 70% of athletes who were overhydrated did not develop EAH. Why is it that only a percentage of athletes develop EAH? What are the factors that protect these athletes from developing EAH? An intriguing possibility discussed by Noakes *et al.* (34) is that some athletes are able to mobilize sodium from internal stores that otherwise are osmotically inactive. This exchangeable sodium store has been described by Edelman and colleagues, Titze and colleagues, and Heer and colleagues (81–86). For example, in the study by Heer *et al.* (86) participants were fed a diet of varying sodium amounts with a fixed amount of water ingestion. Despite these conditions, serum sodium levels

remained constant without a concomitant increase in TBW. These studies indicated that up to one fourth of the total body sodium may exist in bone and cartilage stores that are not osmotically active (*i.e.*, in an insoluble crystal compound) but potentially recruitable into an osmotically active form (81–83). In rats, this nonosmotically active sodium may reside bound to skin proteoglycans (87,88). This dynamic pool of exchangeable sodium also can lead to the osmotic inactivation of sodium if sodium moves into this compartment. This concept was explored indirectly in early studies of syndrome of inappropriate ADH secretion (SIADH) (89,90). In these studies, the balance of sodium loss and water gain could not explain adequately the extent to which serum sodium was reduced. Therefore, it was hypothesized that hyponatremia was related to the osmotic inactivation (sequestration) of previously osmotically active sodium. It should be pointed out that the presence of this exchangeable sodium store is not supported by all investigators. Seelinger *et al.* (91) showed in sodium balance studies in dogs that the changes in TBW and electrolyte levels can be accounted for without invoking an osmotically inactive sodium pool. Furthermore, most of the experimental data supporting an exchangeable osmotically inactive sodium pool are derived from studies on sodium loading that occurs over a more extended period and may not be applicable to the situation that is encountered by athletes. However, the data presented by Noakes *et al.* (34) do support that an exchangeable sodium pool may serve as a buffer for losses of sodium that occur through sweat or urine and also can buffer changes in serum sodium levels that occur with changes in TBW. Therefore, athletes who gain TBW and maintain a normal serum sodium concentration are able to mobilize this store of exchangeable sodium, whereas athletes who develop EAH either cannot mobilize the exchangeable pool or sodium or may osmotically inactivate sodium (34). The factors that govern the exchange of sodium between these compartments is unknown but may involve hormonal factors such as angiotensin II or aldosterone (81–86). The magnitude of this effect in athletes is large with up to 700 mmol of sodium being mobilized from the osmotically inactive pool in the calculations by Noakes *et al.* (34).

Another possibility that may explain the discrepancy between weight gain and the development of hyponatremia is the contribution of water that remains in the lumen of the gastrointestinal tract. This is especially important in athletes who may have consumed a large amount of fluid toward the end of a race and in those with elevated AVP levels. In this setting, rapid absorption of this hypotonic fluid coupled with impaired free water excretion would lead to a rapid fall in serum (especially arterial) sodium levels.

Clinical Features

The clinical manifestations of EAH range from no or minimal symptoms to severe encephalopathy, seizures, respiratory distress, and death. In general, the degree of clinical symptoms is related not to the absolute measured level of serum sodium but to both the rate and the extent of the drop in extracellular tonicity. However, individual variability in the clinical manifestations of hyponatremia is great. It seems that the majority of runners with EAH have mild (weakness, dizziness, headache, nausea/vomiting) or no symptoms (usually associated with serum sodium values ranging from 134 to 128 mmol/L) (1,9–13,15). In athletes with serum sodium values <126 mmol/L, there is a higher likelihood of severe clinical manifestations such as cerebral edema, altered mental status, seizures, pulmonary edema, coma, and death (11,17,19,20,24). However, a systematic survey of symptoms that are associated with hyponatremia in athletes has not been performed.

Hew *et al.* (10) examined the clinical manifestations of 21 hyponatremic runners who finished the Houston Marathon in 2000. These clinical manifestations were compared with those of runners who did not have hyponatremia and presented to the medical tent at the conclusion of the race. The only symptom that was more common ($P = 0.03$) in the hyponatremic group was vomiting. Other symptoms such as headache, nausea, dizziness, and lightheadedness could not distinguish hyponatremia from other causes, attesting to the nonspecific nature of signs and symptoms that are associated with hyponatremia.

A common scenario for medical personnel who staff endurance athletic events is the care of the "collapsed athlete." Several studies have examined the incidence of hyponatremia in this cohort, and a range of 6 to 30% of these athletes had serum sodium values below normal (9,10,12,15–25). The wide range of incidence likely reflects differences in fluid replacement guidelines that were prevalent at the time and place of the study.

Given the difficulty in using clinical symptoms to identify athletes with hyponatremia and the potential for life-threatening consequences, recommendations have been made that medical facilities at endurance events have the capability for onsite analysis of serum or plasma sodium (14). Any athlete who presents with signs or symptoms that are compatible with hyponatremia should be screened for EAH by direct measurement of serum or plasma sodium.

It is critically important to realize that a postrace venous serum sodium measurement may underestimate significantly the severity of hyponatremia (92). This occurs for three reasons: (*1*) Water may be retained in the gastrointestinal tract during the athletic event only to be absorbed rapidly in the postrace period. If AVP levels are elevated, this retained water can lower rapidly the serum sodium when reabsorbed into the circulation. (*2*) Shafiee *et al.* (93) demonstrated that the arterial sodium concentration can be significantly lower than the venous sodium concentration, with this difference being accentuated with more rapid absorption of water (there may be as much as a 4-mM difference between arterial and venous sodium concentrations when water is ingested rapidly). Because it is the arterial sodium concentration that determines the risks for acute central nervous system symptoms, runners with a large amount of retained water in the gastrointestinal tract may be at higher risk for cerebral edema than their venous serum sodium concentration would indicate. Therefore, in athletes with low body mass, mildly depressed venous sodium concentrations, and recent large water intakes, the risk for deterioration secondary to worsening hyponatremia may go unrecognized. (*3*) There may be transient rises in venous sodium concentration at the end of a race (especially if sprinting) as muscle lactic acid

accumulates and leads to a shift of water intracellularly (94). This transient rise in serum sodium can be as high as 10 mM and may mask significant hyponatremia.

Prevention of EAH

Because EAH primarily develops by consumption of fluid in excess of urinary and sweat losses, most efforts at prevention have been focused on education about the risks of the overconsumption of fluids (14,95). In many respects, EAH can be viewed as an iatrogenic condition because of the prevailing view that exercising athletes should drink as much fluid as tolerable during a race. Given that there is a wide variation of sweat production and renal water excretory capacity both between individual athletes and in the same individual depending on ambient conditions during the race, universal guidelines for prevention are not feasible. However, several general recommendations for the prevention of EAH have been made (14,95–98). The first is to drink only according to thirst and no more than 400 to 800 ml/h (95). The higher rates of fluid intake would be recommended for runners with higher rates of exertion (*e.g.*, heavier runners, warmer conditions, longer times of exertion). This rate of fluid intake is well below the levels of intake that are seen in athletes who develop EAH (up to 1.5 L/h water) but above the level that would be associated with dehydration. The second recommendation is to use the USA Track and Field guidelines or other methods to estimate hourly sweat losses during exercise and avoid consuming amounts that are greater than this amount during endurance events (96,97). This is facilitated by serial measurements of weights during and after exercise with the goal to maintain weight or even finish exercise with a slighter lower weight. However, this is difficult, time-consuming, and less likely to be followed by casual athletes. That these recommendations can be effective was demonstrated by Speedy *et al.* (99), who were able to show that prerace education and limiting fluid availability at a race were able to reduce the incidence of hyponatremia without deleterious effects.

Currently, there is insufficient evidence to support the suggestion that ingestion of sodium prevents or decreases the risk for EAH; neither is there any evidence that consumption of sports drinks (electrolyte-containing hypotonic fluids) can prevent the development of EAH (1,35–38,42,100,101). Again, most commercial sports drinks are hypotonic with a sodium content of 10 to 20 mmol/L (230 to 460 mg/L). Overconsumption of such fluids may decrease the rate of serum sodium decline but is unlikely to prevent EAH (35–38,42,100–102). Currently, the American College of Sports Medicine recommends an intake of 0.5 to 0.7 g sodium/L of water as the appropriate level of sodium intake to replace the sodium that is lost in sweat during endurance events (6).

Therapy of EAH

Ideally, medical facilities at endurance events should be able to measure serum or plasma sodium concentrations in any athlete who manifests symptoms that are compatible with EAH or EAHE. However, this may not be universally feasible, and caregivers may have to act empirically on the suspicion of EAH or EAHE as the cause of symptoms. It is crucial for on-site caregivers to be vigilant for the possibility of EAH and not diagnose incorrectly volume depletion and implement a reflex therapy of normal saline infusion.

In 2005, a consensus panel made specific recommendations for the treatment of EAH and EAHE (14). The specific treatment recommended depends on the level of symptoms that the athlete is exhibiting at the time of presentation. Most forms of mild hyponatremia (serum [Na] 130 to 135 mmol/L) will be asymptomatic and found only by laboratory testing. Most athletes with mild, asymptomatic hyponatremia will require only fluid restriction and observation until spontaneous diuresis occurs. It is important that hydration with intravenous 0.9% sodium chloride (NS) be used with utmost caution because this therapy runs the potential risk for further decreasing the serum sodium if AVP levels remain elevated in some athletes (103). Furthermore, the absorption of large amounts of retained hypotonic fluids in the gastrointestinal tract may continue to lower the serum sodium for some time after the event is finished. Therefore, intravenous hydration with NS should be reserved for athletes who manifest clear clinical signs of volume depletion and used cautiously with mandatory monitoring of serum sodium levels (20). Furthermore, cases of pulmonary edema have been described in individuals who received aggressive hydration with 0.9% NS (21). Monitoring of urinary sodium and potassium concentrations and calculation of the urinary free water excretion rate can be helpful in this situation. Athletes who are excreting free water can be monitored safely without need for intravenous fluids, whereas athletes with a negative free water clearance should not receive 0.9% NS because this may worsen the hyponatremia.

The treatment of severe (serum [Na] $<$120 mmol/L) or symptomatic EAH requires the administration of hypertonic saline (11,104–106). There are some important considerations when deciding to treat EAH with hypertonic saline. First is the assumption that all EAH is acute ($<$48 h). This allows the correction of the hyponatremia to be done rapidly and safely (107,108). The second consideration is that no cases of osmotic demyelination syndrome have been reported with the treatment of EAH (14). In the case series by Ayus *et al.* (11), six of seven marathon runners were treated with hypertonic saline for hyponatremia, cerebral edema, and noncardiogenic pulmonary edema. All six of the athletes who received hypertonic saline made a full recovery. Of the five athletes who had follow-up magnetic resonance imaging scans obtained 1 yr after treatment, all were normal. The one athlete who was not treated with hypertonic saline died.

There is no general consensus on the amount of hypertonic saline to be given in athletes with EAH. In the field, it has been suggested that experienced medical staff may give 100 ml of 3% saline over 10 min (14,106). This has been suggested to be safe, raising the serum sodium concentration 2 to 3 mmol/L in a short period of time, and should be used in athletes who exhibit symptoms of severe hyponatremia (confusion, vomiting, respiratory insufficiency) (11,106). The use of hypertonic saline has been shown to induce a greater-than-expected increase in the serum sodium, likely as a result of a decrease in AVP, and the

restoration of a dilute urine; therefore, it is imperative that all athletes who receive therapy for EAH or EAHE be transported to a medical center where the serum sodium can be monitored closely (11,14,106,107). Use of hypertonic saline should be continued in the hospital to correct the hyponatremia using standard protocols. In general, 3% hypertonic saline can be given at 1 to 2 ml/kg per h with close monitoring of both serum electrolytes and urinary sodium and potassium excretion. In cases of severe antidiuresis, the rate of infusion may need to be increased to 3 to 4 ml/kg per h. Once significant water diuresis begins, the rate of infusion can be decreased or stopped. Special mention should be made of the patient who presents with severe EAHE and pulmonary edema. It is imperative that these patients receive emergent therapy with 3% hypertonic saline despite evidence of volume overload. As described by Ayus *et al.* (21), patients who do not receive hypertonic saline have poor outcomes. The addition of a loop diuretic can be considered in two circumstances: (*1*) Significant volume overload and (*2*) significant antidiuresis with a very elevated urinary osmolality, sodium, and/or potassium level.

Recently, selective vasopressin receptor antagonists (VRA) have been developed for the therapy of hyponatremia that is associated with SIADH, cirrhosis, and congestive heart failure (109). These agents include two oral preparations (lixivaptan and tolvaptan) and an intravenous agent (conivaptan). In the phase 2 trial with lixivaptan, patients with SIADH had an increase in serum sodium from 126 ± 5 to 133 ± 5.6 mmol/L after 48 h with concomitant increases in urine flow rate and falls in urine osmolality (110). Conivaptan has the advantage that correction of serum sodium is faster than with the oral agents, likely owing to enhanced bioavailability. In one study with conivaptan, the median time to a 4-mmol/L increase in serum sodium was 23.7 h (111). However, in the treatment of EAH and other forms of acute hyponatremia, the role of these agents is unclear. It is not known whether VRA alone will achieve sufficiently rapid correction of acute, severe hyponatremia without the use of hypertonic saline. As detailed by Greenberg and Verbalis (111), both VRA and hypertonic saline could be used initially. Once there is a small correction in the serum sodium, the hypertonic saline could be stopped and the VRA continued to facilitate water diuresis. One fear of the use of VRA in the treatment of EAH is that athletes could have an extremely rapid water diuresis with the risk for resultant hypernatremia; therefore, these agents are not likely to be useful for the therapy of EAH. Overall, in the therapy of EAH, hypertonic saline remains the therapy of choice.

Hypokalemia can develop during athletic events especially after the event is completed (112). It is important that the potential for hypokalemia be appreciated because it can have important implications for treatment. First, hypokalemia is a risk factor for the development of osmotic demyelination that is associated with correction of chronic hyponatremia (113). Whether hypokalemia is a risk factor for poor neurologic outcomes that are associated with therapy for acute hyponatremia is not known. Second, replacement of potassium deficits will increase the serum sodium as sodium shifts out of cells. With concomitant potassium repletion, the serum sodium may rise faster than anticipated, and correction of hyponatremia should be less aggressive (108).

Conclusion

EAH and EAHE are potentially devastating complications of endurance events that occur in otherwise healthy, active, and young individuals. The pathophysiology of this condition includes multiple intersecting pathways that include both environmental (overabundance of fluids and recommendations for overdrinking) and innate physiologic control systems. When appropriately recognized, EAH and EAHE can be treated effectively with a low rate of morbidity and mortality. However, when not recognized, this condition can be fatal. Fortunately, preventive measures that stress judicious use of fluid replacement during exercise are effective and should be widely publicized and implemented.

Disclosures

None.

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