CASE REPORT

Three Cases of Severe Hyponatremia During a River Run in Grand Canyon National Park

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We present 3 cases of severe hyponatremia occurring on a commercially guided river rafting trip on the Colorado River in Grand Canyon National Park. All 3 women appeared to have been overhydrating because of concern about dehydration and required evacuation within 24 hours of each other after the staggered onset of symptoms, which included fatigue and emesis progressing to disorientation or seizure. Each was initially transferred to the nearest hospital and ultimately required intensive care. Imaging and laboratory data indicated all 3 patients had hypervolemic hyponatremia. Unlike the well-documented exercise-associated hyponatremia cases commonly occurring in prolonged endurance athletic events, these 3 unique cases of acute hyponatremia were not associated with significant exercise. The cases illustrate the diagnostic and treatment challenges related to acute hyponatremia in an austere setting, and underscore the importance of preventive measures focused on avoidance of overhydration out of concern for dehydration.

Key words: arginine vasopressin, exercise, exercise-associated hyponatremia, hypertonic saline, hyponatremia, sodium, syndrome of inappropriate ADH secretion, water-electrolyte imbalance

Introduction

Exercise-associated hyponatremia (EAH) is known to be a possible complication of endurance athletic activities and military training exercises that may have a fatal outcome.^{1–5} It is now recognized that the underlying pathophysiology of EAH involves overhydration.^{6,7} Hypervolemic hyponatremia has also been reported among persons participating in lower intensity activities such as hiking^{8–15} and Bikram yoga,¹⁶ and while awaiting rescue from a fall into a crevasse.¹⁷ Here, we describe 3 cases of severe hyponatremia developing within a 2-day period on a single commercially guided river rafting trip through Grand Canyon National Park.

A Colorado River trip through Grand Canyon is perhaps the premier whitewater river trip in the world. Renowned for its rapids, scenery, and remoteness, the Colorado River in Grand Canyon is 446 km long. Along its course, the Colorado River drops more than 670 m in elevation and essentially splits the 486,000 hectare Grand Canyon

National Park in half. River runners may travel down the Colorado River on professionally guided (commercial) trips or on self-guided (noncommercial or private) trips. Trips with large motorized pontoon rafts average 7 to 9 days to travel the entire distance and navigate more than 160 rapids, whereas smaller oar-powered boats average 13 to 18 days. Each year roughly 25,000 people run the river through Grand Canyon, 17,000 as commercial passengers and nearly 8,000 on self-guided trips.¹⁸

The Grand Canyon is located entirely in northern Arizona, and desert conditions exist in the canyon bottom, as much as 1520 m below the rim. Daytime high temperatures average near 40°C during the summer months and can reach more than 50°C. Entry or exit from the canyon is only achieved either by lengthy foot travel on isolated trails and routes or by helicopter for the majority of its length. As a result, nearly all emergency evacuations off the river are made by helicopter.

Case Presentations

RIVER TRIP AND PATIENT EVACUATIONS

The river trip launched mid-morning on June 11, 2006, in an 11-m motorized pontoon raft for 7 days of travel

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through the Canyon. Aboard were 17 passengers and 3 river guides. The weather was dry, hot, and sunny, with a high temperature of 40.5°C. Guides instructed the passengers to drink plenty of water, and passengers were encouraged to wear rain gear during rapids to prevent getting wet and cold from the 8.8°C dam-released Colorado River water.

The first day was uneventful, but by mid-afternoon on the second day, the first patient began feeling unwell, with fatigue and stomach discomfort. The morning had included 2 short (<2 km) hikes, but she opted out of the second hike. The guides believed she had not been drinking enough and was experiencing dehydration and heat exhaustion. She and all other passengers were strongly advised to drink more water supplemented with an electrolyte drink mix (Hydralyte, 45 to 55 mEq/L of sodium) and to eat salty snacks.

At noon on the third day, a stop was made where a ranger station is located for the first patient to be evacuated by helicopter because she was feeling worse and had been having emesis and diarrhea. After her evacuation, the river trip continued downstream. Less than 2 hours later, the second patient suddenly became disoriented and had a grand mal seizure while on the boat. She, too, was evacuated by helicopter. Shortly thereafter, the river trip made camp for the evening, and the third patient abruptly began to vomit and became unresponsive. Unable to secure safe evacuation because of darkness, she remained comatose at camp, and was monitored by the river guides. She was evacuated by helicopter at dawn on the fourth day of the trip. The others remaining on the river finished the trip uneventfully 3 days later.

PATIENT PREHOSPITAL AND HOSPITAL CLINICAL HISTORIES

Patient 1

The first patient, an overweight (73 kg) 67-year-old woman, had a medical history significant for hypertension treated with hydrochlorothiazide and enalapril. She had no rafting experience. She slipped and fell into the water at the river's edge during the first night while urinating, but was uninjured. Mid-afternoon on the second day of the trip, she began complaining of feeling "tired and full" and reportedly had not urinated for some time. She was given bananas, almonds, and crackers and encouraged to consume an electrolyte drink. She began vomiting and having diarrhea that evening. She was given more electrolyte drink, salted crackers, and pita bread. She slept poorly and vomited again during the night, and guides continued to encourage her to drink more of the electrolyte drink and eat crackers.

Neither total fluid intake nor extent of fluid loss through vomiting and diarrhea was documented.

On the morning of the third day of the trip, she was still feeling tired and weak, and the river guides decided she should be evacuated. Several hours later and 45 km further downstream, she was wheeled by litter nearly 1 km to a remote backcountry ranger station staffed by an emergency medical services-trained ranger. Upon arrival at approximately noon, she was noted to be "shaking all over" despite the 41.1°C heat. A medical evacuation by National Park Service (NPS) helicopter was requested. The NPS flight paramedic found her alert and oriented with a Glasgow Coma Scale (GCS) of 15. She was hypertensive at 175/85 mm Hg and had a heart rate of 80 beats/minute. An electrocardiogram (ECG) was unremarkable. An intravenous (IV) line was established with 0.9% normal saline infused at a maintenance rate. She was flown out and initially transported to Grand Canyon Clinic on the rim. There, she appeared alert and was oriented, but somewhat confused when answering questions, anxious, and repeating phrases. The remainder of her neurologic examination was nonfocal. She remained hypertensive, with her systolic blood pressure in excess of 180 mm Hg. Her serum sodium concentration was 114 mEq/L. Other laboratory values are shown in the [Table](#). She was started on an IV drip with a total of 600 mL normal saline infused as she was helicoptered for admission to the nearest hospital 145 km away.

Upon arrival at the emergency department, her serum sodium concentration was slightly higher at 119 mEq/L. Her initial oxygen saturation was 92% on room air, heart rate was 87 beats/minute, and blood pressure was 193/75 mm Hg. The physical examination showed neurologic deterioration, with significant agitation, confusion, and disorientation. Also noted were dry mucous membranes, a slightly distended abdomen, and slightly flushed and dry skin. The ECG and head computed tomography scan were unremarkable. She was given lorazepam and droperidol, and received a total of 1500 mL IV normal saline. A Foley catheter returned 1500 mL clear urine. Her oxygen saturation on room air deteriorated to 77%, improving to above 90% with 15 L of oxygen by non-rebreather mask. She was intubated and admitted to the intensive care unit (ICU) for further care. At this point, her serum sodium had improved to 123 mEq/L. She was treated with an unknown volume of IV normal saline, and was discharged from the ICU approximately 36 hours after admission, with normal serum sodium and potassium concentrations and a normal mental status. She went on to fully recover uneventfully.

Patient 2

This 72-year-old, overall healthy woman weighing approximately 70 kg had a medical history significant

Table. Initial blood chemistry analyses for the 3 patients

<i>Chemistry (normal range)</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>
Sodium (135–145 mEq/L)	114	126	114
Potassium (3.5–5.5 mEq/L)	4.2	3.1	3.8
Chloride (98–108 mEq/L)	83	87	84
Glucose (70–110 mg/dL)	134	141	116
Blood urea nitrogen (8–23 mg/dL)	9	...	10
Creatinine (0.7–1.2 mg/dL)	...	...	0.5
Hematocrit (37%–47%)	39	WNL	35.6
Hemoglobin (12–17 g/dL)	13.3	WNL	...
Troponin (0–0.05 ng/mL)	...	<0.05	Negative
Creatine kinase (21–215 IU/L)	...	2000	727
Predicted serum osmolality (275–295 mOsm/kg)	240	261	239

WNL, within normal limits.

for only insomnia treated with zolpidem. She also had no rafting experience. On the second day of the trip, she participated in the short hikes. She slipped and fell during the night while urinating, injuring her wrist, which was splinted. On the third day of the trip, because of her wrist injury, she was offered an NPS helicopter flight out of the canyon along with the first patient; however, she declined. As the trip headed downstream, she wore a thick, heavy wetsuit to protect against the cold Colorado River despite the 41°C temperatures in the Canyon that day. Family members reported to the guides that she had been drinking “plenty” of water; however, no quantity was documented. At mid-afternoon that day, less than 2 hours after the evacuation of the first patient, she complained of being tired, and it was noted that she did not appear well. She then became acutely confused and disoriented, began vomiting, had a grand mal seizure, and then became unresponsive, with shallow and labored breathing. The guides requested emergency assistance from the NPS, and the patient was evacuated by NPS helicopter directly to the same hospital where patient 1 was transferred. En route, she was sedated with midazolam and received 1300 mL IV normal saline. She remained unresponsive throughout the flight.

Upon arrival to the hospital, the patient presented as unresponsive with no purposeful movements. Initial physical examination was otherwise unremarkable, showing clear lung sounds and a soft, nondistended abdomen. She was intubated and placed on mechanical ventilation. Her initial blood pressure in the emergency department was 230/116 mm Hg. Initial serum sodium concentration was 126 mEq/L. Other laboratory values are shown in the [Table](#). A Foley catheter was placed, resulting in an immediate output of 2000 mL clear, yellow urine. Chest radiograph, head computed tomography scan, and ECG were unremarkable. She was treated with lorazepam and labetalol, with

improvement in her blood pressure. She was then transferred by ground ambulance to another hospital 2.5 hours away for ICU admission. Upon admission, her serum sodium concentration was 122 mEq/L. She was treated with IV normal saline, and within 12 hours, she was weaned off the ventilator and extubated. Physical examination shortly after extubation revealed an alert and oriented patient, neurologically intact, complaining of right wrist tenderness. The intensivist observed significant diuresis during her stay. The patient was also noted to have a stable wrist fracture at the base of the scaphoid that was treated with a splint. The patient continued to improve and was discharged with normal mental status and normal serum sodium and potassium concentrations approximately 72 hours after admission.

Patient 3

The third patient, a 68-year-old woman who was also an inexperienced rafter, had no significant medical history or medication use. After making camp for the evening of the third day of the trip after the evacuations of the first 2 patients, she began vomiting. She complained of being tired and having slept poorly the previous 2 nights because she had been up urinating often throughout the night. Unable to eat dinner, she attempted to lie down to sleep. Shortly afterward, she was found minimally responsive to voice or painful stimuli. Guides reported her eyes were glazed and teeth were clenched. Emergency helicopter evacuation was requested from NPS but denied owing to the extremely hazardous night flying conditions in Grand Canyon. The patient was placed in a recovery position for airway monitoring as she continued to vomit throughout the night. She was incontinent and appeared cyanotic. She was evacuated by helicopter in the early hours of the morning of the fourth day of the trip.

The helicopter flew the patient to the same hospital where patient 1 was in the ICU. En route, the flight crew reported seizure activity and noted that the patient was unconscious and diaphoretic, and became more obtunded in flight, with a GCS of 7. Upon arrival to the hospital, she presented with an initial serum sodium concentration of 114 mEq/L. Other laboratory values are shown in the [Table](#). Initial blood pressure was 134/66 mm Hg and heart rate was 101 beats/minute. Room air oxygen saturation on arrival was 80%. Initial physical examination revealed an unresponsive patient with a GCS of 8 and 4-mm pupils, equal and reactive. She had no gag reflex but responded to painful stimuli, withdrawing both upper and lower extremities. Her abdomen was soft and nontender. She was intubated and admitted to the ICU. Head computed tomography scan was negative, and chest radiograph showed a right perihilar infiltrate. The ECG was unremarkable except for a left bundle branch block. The patient was treated with 2 mg lorazepam to prevent further seizures, and a propofol drip was started to manage her agitation. Intravenous normal saline was administered at 150 mL/h. She was also given 250 mL IV 3% hypertonic saline over 4 hours. Within 2 hours, she experienced spontaneous diuresis of approximately 900 mL urine. She was successfully extubated approximately 24 hours after admission to the ICU, and discharged, fully recovered, less than 40 hours later.

Discussion

These 3 cases of severe hyponatremia during a single river rafting trip are an extraordinary illustration of the potential adverse effects of overhydration. Each case was associated with minimal physical exertion and presented similarly to other cases previously reported in which minimal exertion was involved and overhydration appeared to be a primary underlying cause of the hyponatremia.^{11,16,17,19,20} It is now known that fluid retention from secretion of arginine vasopressin (AVP) due to nonosmotic stimuli^{6,7} and excessive loss of urine sodium from secretion of brain natriuretic peptide^{20–22} contribute to the pathophysiology of EAH. It is not clear whether these hormones play a role in the pathophysiology of acute hyponatremia when minimal exertion is involved. Considering, however, that nausea, vomiting, pain (the fall of patient 2 with resultant wrist fracture), and emotional stress (uncomfortable environment from extreme heat, sleep deprivation, anxiety about rapids, stress of seeing friends evacuated, and so forth) are nonosmotic stimuli for secretion of AVP,^{23–25} one could hypothesize that the hormone might have contributed to the development of hyponatremia in the 3 women described here.

It is likely that these women overhydrated to avoid dehydration—a rational concern when exposed to the high ambient temperatures of Grand Canyon in the summer. The river guides had frequently warned passengers about the dangers of dehydration, and later confirmed that each woman was drinking as instructed on the boat and in camp. Further contributing to overhydration was an uncertainty among the guides as to whether the women were dehydrated or overhydrated once they became symptomatic. Accurate field assessment of hydration status can be confounded by oliguria resulting from AVP secretion in the presence of overhydration.⁶ That may have been the case with patient 1, who reportedly had not urinated for some time when she began feeling “tired and full,” the latter symptom possibly due to overhydration. Although actual fluid intake was not documented, the emphasis on avoiding dehydration and high fluid intake history, the report of urinary frequency (patients 2 and 3) during the early part of the trip, and the low admission blood urea nitrogen and predicted serum osmolality support excessive fluid intake by the women. It is now recognized that a key strategy for preventing hyponatremia is to avoid overhydration by drinking to thirst.^{6,7}

Whether excessive sodium loss and inadequate sodium intake played a role in the development of hyponatremia in these cases cannot be ascertained with certainty. It is indeed likely that the hot environmental conditions combined with the wetsuits and occlusive rain suits worn by the women contributed to sodium loss through sweating. Furthermore, the nausea and gastrointestinal symptoms causing poor food intake by all 3 women would have affected sodium intake. Nevertheless, prior evidence from endurance activities has suggested that sodium supplementation during exercise does not affect serum sodium concentration,^{26–28} nor does it prevent hyponatremia when a person is overhydrating.^{29,30} Therefore, we suspect that excessive sodium loss or inadequate intake were not important contributing factors to the development of hyponatremia among these women, especially given that symptomatic hyponatremia began within the first few days of exposure to high temperatures.

Because all 3 of the cases we report were women, one might question whether sex influences may have also contributed to the development of hyponatremia. Early work suggested that women might be more susceptible to EAH than men, but it is now recognized that it is smaller persons who are following fluid intake guidelines designed for larger persons who are at greater risk.⁶ It is for this reason that women appear to be at higher risk for hyponatremia, consistent with the observation in Grand Canyon National Park, where women have been affected by hyponatremia much more frequently than men.^{8,9}

Heat-related illnesses have been of serious concern at Grand Canyon National Park for many years. Deaths due to heat illnesses have far exceeded those from hyponatremia; there are 42 known cases of the former, as well as 33 additional deaths from cardiac arrest, while hiking in hot weather to which heat stress likely contributed, versus 1 confirmed death from hyponatremia.³¹ Furthermore, for every heatstroke death in Grand Canyon, there have been hundreds of cases of dehydration and heat exhaustion. Therefore, instituting preventive measures to reduce the risk of heat illnesses among Grand Canyon visitors is an important mission.

Heat illness prevention programs—namely, the Preventive Search and Rescue Program—in Grand Canyon National Park were initiated in 1997¹² and largely focused on educating visitors to avoid dehydration. The catalysts for this preventive form of education were 5 heat-related deaths and dozens of heat exhaustion cases among the nearly 500 search and rescue missions during the summer of 1996, taxing the rescue resources of Grand Canyon National Park. This was a time when maintenance of hydration during exercise was universally promoted.⁴ Hyponatremia among Grand Canyon hikers had already been documented,^{8,9} and it was also recognized to occur among Grand Canyon river runners beginning in the early 1990s, with a frequency of roughly 1 or 2 cases per year through the decade. Coinciding with the enhanced effort to reduce the risk of dehydration, hyponatremia cases peaked throughout Grand Canyon in the 1990s. Grand Canyon search and rescue records show a record high of 28 documented cases of hyponatremia in 1998. Fortunately, recent efforts to more appropriately educate visitors about the potential adverse effects of overhydration, including new signage in 2013 reflecting current recommendations to drink to thirst,^{6,7} have been associated with a decrease in number of hyponatremia cases to approximately half of the highest frequency recorded during the 1990s. From Grand Canyon emergency medical services reports, there was only 1 case of hyponatremia involving river runners from 2011 through 2013.

As for other preventive measures for heat-related illness, current recommendations for Grand Canyon visitors include the use of frequent rest breaks when hiking. Rest breaks from exertion (encouraged for 10 minutes every hour) will reduce metabolic heat generation, and may also mitigate AVP secretion.²² Minimizing anxiety and regular cooling may also limit AVP secretion.²² Of course, heat acclimation should be done before an extended hike or river trip in Grand Canyon. The role of sodium intake in prevention of heat illness and hyponatremia in Grand Canyon is less clear. Sodium supplementation does not appear valuable in

maintaining either serum sodium concentrations or hydration levels,^{26–28,32} or in preventing hyponatremia when the person is overhydrating during endurance sports activities,^{29,30} nor was an emphasis on intake of salty snacks preventive of hyponatremia with overhydration in the present cases.

Progress has been made relative to field diagnosis and treatment of hyponatremia in Grand Canyon National Park, although some challenges remain. Early signs and symptoms of hyponatremia are nonspecific (headache, nausea, vomiting, fatigue) and can be confused with dehydration, especially when concomitant oliguria from AVP secretion is present. That poses a conundrum as the treatments for these two illnesses are radically different and essentially opposite. To distinguish between the two when laboratory testing is unavailable, an accurate history of total fluid intake is the single most important piece of information to obtain. Unfortunately, hydration status depends on several factors in addition to fluid intake, including body size, sweat rate, exercise intensity, and ambient conditions, so the field determination of overhydration is not always straightforward. Fortunately, Grand Canyon rangers are currently able to make more accurate assessments with point-of-care blood chemistry analyzers, which were first used in the backcountry in 1997 and have subsequently become more readily available.

Treating hyponatremia, especially in an austere setting, also poses a significant challenge. Restriction of further isotonic or hypotonic fluid intake is imperative.^{6,7} It may seem paradoxical, but although sodium supplementation may not prevent hyponatremia associated with overhydration, concentrated oral hypertonic solutions have been shown to effectively elevate serum sodium concentration^{33–35} and provide symptomatic relief of moderate hyponatremia.³⁵ Boullion cubes (2 in ~100 mL water provides ~80 mEq sodium) have been used in the Grand Canyon backcountry to create hypertonic solutions. Foods high in sodium content have also been used as a substitute if creating an oral hypertonic solution is impractical or impossible. If there are no mental status changes, ongoing fluid restriction and monitoring over several hours may be necessary to allow for spontaneous diuresis and self-correction of serum sodium concentrations. However, when patients have progressed into an altered mental status or encephalopathy, oral correction becomes impractical and treatment with as many as three 100-mL IV boluses of 3% hypertonic saline has been recommended.^{6,7} Use of oral and IV hypertonic saline has been regular practice in Grand Canyon National Park since 2012. Attempted treatment of acute hyponatremia with isotonic fluids has been well demonstrated to be less effective and

potentially dangerous,^{1,5,11,15,16,20,29,36} so is no longer used in Grand Canyon for known or presumed hyponatremia, and should also be avoided in the early hospital management.

Conclusion

Acute hyponatremia is now recognized to be a risk during various wilderness activities across a range of physical activity levels when fluid overconsumption is involved. The present cases are a remarkable demonstration of overhydration resulting in hyponatremia during a wilderness activity that involved minimal physical exertion. As is the situation with EAH, we suggest that hormonal influences causing water retention may have also played a role in the pathogenesis of these cases. Preventive measures are essential, and require a balance in which dehydration and overhydration are both avoided. When preventative measures have failed, symptomatic acute hyponatremia requires proper recognition and field treatment with hypertonic saline to enhance survival.

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References

1. Ayus JC, Varon J, Arief AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med.* 2000;132:711–714.
2. Gardner JW. Death by water intoxication. *Mil Med.* 2002;167:432–434.
3. Garigan TP, Ristedt DE. Death from hyponatremia as a result of acute water intoxication in an Army basic trainee. *Mil Med.* 1999;164:234–238.
4. Noakes T. *Waterlogged: The Serious Problem of Overhydration in Endurance Sports.* Champaign, IL: Human Kinetics; 2012.
5. Siegel AJ, Verbalis JG, Clement S, et al. Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. *Am J Med.* 2007;120:461.e11–17.
6. Bennett BL, Hew-Butler T, Hoffman MD, Rogers IR, Rosner MH. Wilderness Medical Society practice guidelines for treatment of exercise-associated hyponatremia. *Wilderness Environ Med.* 2013;24:228–240.
7. Hew-Butler TD, Ayus JC, Kipps C, et al. Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. *Clin J Sport Med.* 2008;18:111–121.
8. Backer HD, Shopes E, Collins SL. Hyponatremia in recreational hikers in Grand Canyon National Park. *J Wilderness Med.* 1993;4:391–406.
9. Backer HD, Shopes E, Collins SL, Barkan H. Exertional heat illness and hyponatremia in hikers. *Am J Emerg Med.* 1999;17:532–539.
10. Basnyat B, Sleggs J, Spinger M. Seizures and delirium in a trekker: the consequences of excessive water drinking? *Wilderness Environ Med.* 2000;11:69–70.
11. Coler C, Hoffman MD, Towle G, Hew-Butler T. Hyponatremia in an 85-year-old hiker: when depletion plus dilution produces delirium. *Wilderness Environ Med.* 2012;23:153–157.
12. Noe RS, Choudhary E, Cheng-Dobson J, Wolkin A, Newman S. Exertional heat-related illnesses at the Grand Canyon National Park, 2004–2009. *Wilderness Environ Med.* 2013;24:422–428.
13. Rothwell SP, Rosengren D. Severe exercise-associated hyponatremia on the Kokoda Trail, Papua New Guinea. *Wilderness Environ Med.* 2008;19:42–44.
14. Shopes EM. Drowning in the desert: exercise-induced hyponatremia at the Grand Canyon. *J Emerg Nurs.* 1997;23:586–590.
15. Spano SJ, Reagle Z, Evans T. Symptomatic hypotonic hyponatremia presenting at high altitude. *Wilderness Environ Med.* 2014;25:69–74.
16. Reynolds CJ, Cleaver BJ, Finlay SE. Exercise associated hyponatraemia leading to tonic-clonic seizure. *BMJ Case Rep.* 2012;2012. <http://dx.doi.org/10.1136/bcr.08.2012.4625>.
17. Zafren K. Hyponatremia in a cold environment. *Wilderness Environ Med.* 1998;9:54–55.
18. Grand Canyon National Park. River and weighted lottery FAQs. Available at: http://www.nps.gov/grca/planyourvisit/upload/river_and_weighted_lottery_faqs.pdf. Accessed April 12, 2014.
19. Gutmann FD, Gardner JW. Fatal water intoxication of an Army trainee during urine drug testing. *Mil Med.* 2002;167:435–437.
20. Zelingher J, Putterman C, Ilan Y, et al. Case series: hyponatremia associated with moderate exercise. *Am J Med Sci.* 1996;311:86–91.
21. Harris G, Reid S, Sikaris K, McCrory P. Hyponatremia is associated with higher NT-proBNP than normonatremia after prolonged exercise. *Clin J Sport Med.* 2012;22:488–494.
22. Hew-Butler T, Jordaan E, Stuempfle KJ, et al. Osmotic and non-osmotic regulation of arginine vasopressin during prolonged endurance exercise. *J Clin Endocrinol Metab.* 2008;93:2072–2078.
23. Hew-Butler T, Dugas JP, Noakes TD, Verbalis JG. Changes in plasma vasopressin concentrations in cyclists participating in a 109 km cycle race. *Br J Sports Med.* 2010;44:594–598.

24. Baylis PH, Zerbe RL, Robertson GL. Arginine vasopressin response to insulin-induced hypoglycemia in man. *J Clin Endocrinol Metab.* 1981;53:935–940.
25. Rowe JW, Shelton RL, Helderman JH, et al. Influence of the emetic reflex on vasopressin release in man. *Kidney Int.* 1979;16:729–735.
26. Winger J, Hoffman MD, Hew-Butler T, et al. The effect of physiology and hydration beliefs on race behavior and postrace sodium in 161-km ultramarathon finishers. *Int J Sports Physiol Perform.* 2013;8:536–541.
27. Hew-Butler TD, Sharwood K, Collins M, Speedy D, Noakes T. Sodium supplementation is not required to maintain serum sodium concentrations during an Ironman triathlon. *Br J Sports Med.* 2006;40:255–259.
28. Speedy DB, Thompson JM, Rodgers I, Collins M, Sharwood K, Noakes TD. Oral salt supplementation during ultradistance exercise. *Clin J Sport Med.* 2002;12:279–284.
29. Hoffman MD, Stuenkel KJ, Sullivan K, Weiss RH. Exercise-associated hyponatremia with exertional rhabdomyolysis: importance of proper treatment. *Clin Nephrol.* 2014 Jun 16. [Epub ahead of print].
30. Twerenbold R, Knechtle B, Kakebeeke TH, et al. Effects of different sodium concentrations in replacement fluids during prolonged exercise in women. *Br J Sports Med.* 2003;37:300–303.
31. Ghiglieri MP, Myers TM. *Over the Edge: Death in Grand Canyon.* 2nd ed. Flagstaff, AZ: Puma Press; 2012:558.
32. Hoffman MD, Stuenkel KJ. Hydration strategies, weight change and performance in a 161-km ultramarathon. *Res Sports Med.* 2014;22:213–225.
33. Owen BE, Rogers IR, Hoffman MD, et al. Efficacy of oral versus intravenous hypertonic saline in runners with hyponatremia. *J Sci Med Sport.* 2013;17:457–462.
34. Rogers IR, Hook G, Stuenkel KJ, Hoffman MD, Hew-Butler T. An intervention study of oral versus intravenous hypertonic saline administration in ultramarathon runners with exercise-associated hyponatremia: a preliminary randomized trial. *Clin J Sport Med.* 2011;21:200–203.
35. Siegel AJ, d'Hemecourt P, Adner MM, Shirey T, Brown JL, Lewandowski KB. Exertional hyponatremia in collapsed marathon runners: a critical role for point-of-care testing to guide appropriate therapy. *Am J Clin Path.* 2009;132:336–340.
36. Bennett BL, Hew-Butler T, Hoffman MD, Rogers IR, Rosner MH. In reply to clinical practice guidelines for treatment of exercise-associated hyponatremia. *Wilderness Environ Med.* 2013;24:468–471.