Exercise-associated hyponatraemia (EAH) in South African endurance athletes had become rare since it was first described in three Comrades Marathon runners in 1985. Since that report, educational steps highlighting the potential hazards of overdrinking during endurance exercise minimised the incidence and morbidity of EAH in South African endurance races. However, recently two severe cases of EAH have come to our attention (case 1 from the Comrades Marathon and case 2 from the Argus Cycle Tour) that highlight the need to disseminate the latest evidence-based information, particularly with regard to optimal treatment strategies for EAH.

**Case reports**

**Case 1**
A healthy 28-year-old woman with an unremarkable past medical history and on no medications, running her second 89 km Comrades Marathon, pulled out at 76 km in ~10.5 hours feeling dizzy and weaving across the road. During the race she had followed her normal practice of ingesting a GU packet with 200 ml of water every 45 minutes along with Coke and water *ad libitum* for an estimated fluid consumption rate of ~550 ml/h. She said that she had passed urine four times during the race of ‘good volume’, the last time just under half way (40 km). She had trained exactly the same as the year before (when she had completed the race in a time of 11 hours and 48 minutes), was not injured, and did not take any medications immediately before or during the race. Two weeks before the race, however, she was diagnosed with sinusitis and dispensed ciprofloxacin, the last dose of which was taken two days before the start of the race. She felt well enough to run on race day.

She remembers lying down at the aid station before becoming confused; she then vomited and suffered a grand mal seizure. She was transported via ambulance to the local hospital where a diagnosis of hyponatraemia was confirmed, with a serum sodium concentration of 112 mmol/l associated with pulmonary oedema (bilateral lung crackles) and encephalopathy (Glasgow Coma Scale (GCS) score of 9/15). She was quickly intubated, given a 40 mg bolus of furosemide plus 5 mg diazepam intravenously, and transported to the local intensive care unit (ICU).

In hospital she had three more seizures and was given Ringer’s lactate (250 ml/h), potassium chloride (KCl: 2 ampoules in 200 ml 0.9% saline) and sodium bicarbonate (8.5% for metabolic acidosis). A chest X-ray showed an infiltrate in the right upper lobe. Initial biochemical analyses revealed the following blood concentrations (reference ranges in brackets): sodium (Na⁺) 114 mmol/l (136 - 145 mmol/l); potassium (K⁺) 3.4 mmol/l (3.5 - 5.1 mmol/l); chloride (Cl⁻) 78 mmol/l (98 - 107 mmol/l); bicarbonate (BIC) 11 mmol/l (22 - 29 mmol/l); urea 3.4 mmol/l (1.7 - 8.3 mmol/l); creatinine (creat) 93 µmol/l (49 - 90 µmol/l), creatine phosphokinase (CK)
2 699 U/l (26 - 192 U/l); and white blood cell count (WBC) 23.7 x 10^9/l (3.9 - 9.8 x 10^9/l). Nine hours later, the values were as follows: Na+ 116 mmol/l; K+ 3.8 mmol/l; Cl− 85 mmol/l; BIC 19 mmol/l; urea 2.7 mmol/l; and creat 65 mmol/l. The patient was then switched to 0.9% saline rehydration (200 ml/h) on day 2, presumably in response to minimal clinical and biochemical progress.

With administration of 0.9% saline, a return to ‘normal’ blood Na+ was achieved 18 hours later (Fig. 1a), which was associated with an accumulated positive fluid balance of 2.9 litres (Fig. 1b). By day 4, the accumulated positive fluid balance was 6.3 litres (Fig. 1b), in response to which a 20 mg bolus of furosemide was administered every 6 hours. The patient was extubated on day 4, and urinated copiously on day 5 (Fig. 1a); a documented increase in blood Na+ to 146 mmol/l (hypernatraemia) was documented on day 6 (discharge). An overall accumulated fluid balance of 3.7 litres was noted at discharge. Interestingly, blood CK (day 2 = 10 911 U/l, day 3 = 35 731 U/l, and day 4 = 36 832 U/l) continued to increase through day 4 despite normal creatinine and urea concentrations and calculated glomerular filtration rates (eGFR >90 ml/min).

Case 2
A 25-year-old woman with a past medical history of asthma controlled with salbutamol and recurrent migraines controlled with magnesium was admitted every 6 hours. The patient was extubated on day 4, and urinated copiously on day 5 (Fig. 1a); a documented increase in blood Na+ to 146 mmol/l (hypernatraemia) was documented on day 6 (discharge). An overall accumulated fluid balance of 3.7 litres was noted at discharge. Interestingly, blood CK (day 2 = 10 911 U/l, day 3 = 35 731 U/l, and day 4 = 36 832 U/l) continued to increase through day 4 despite normal creatinine and urea concentrations and calculated glomerular filtration rates (eGFR >90 ml/min).

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Cardiovascular disease (CVD) is a major cause of mortality and morbidity with positive fluid balance (PFB) associated with a higher risk of cardiovascular events. However, no study has examined the effect of CVD on PFB in a high-risk population. The objective of this study was to determine the effect of CVD on PFB in a high-risk population. The study was conducted at a tertiary care hospital in India. The study included 150 patients with CVD and 150 patients without CVD matched for age, sex, and diabetes mellitus. The PFB was calculated as the difference between the net fluid intake and the net fluid output. The PFB was divided into four categories: negative fluid balance (NFB), small positive fluid balance (SPFB), moderate positive fluid balance (MPFB), and large positive fluid balance (LPFB). The results showed that patients with CVD had a higher risk of PFB (odds ratio [OR] = 1.5, 95% confidence interval [CI] = 1.1 - 2.0, p = 0.02). The risk of PFB was higher in patients with CVD who had diabetes mellitus (OR = 2.0, 95% CI = 1.3 - 3.2, p = 0.002). The risk of PFB was also higher in patients with CVD who had hypertension (OR = 1.7, 95% CI = 1.2 - 2.5, p = 0.006). The results suggest that CVD is associated with an increased risk of PFB. Further studies are needed to confirm these findings and to determine the mechanisms underlying the association between CVD and PFB.
initially treated with Ringer’s lactate. In case 1 neither symptoms nor blood Na⁺ improved with such treatment (Fig. 1a), while in case 2 the symptoms worsened appreciably (Table 1), GCS declining from 8/15 to 3T/15). Table 2 compares the ionic composition of commonly used intravenous fluids in critical care settings and highlights the improved mathematical efficacy of hypertonic versus isotonic saline solutions in raising blood Na⁺. Isotonic fluid administration is further discouraged in hyponatraemic patients with inappropriate arginine vasopressin secretion. In the syndrome of inappropriate antidiuretic hormone secretion (SIADH), most of the sodium that is administered intravenously is promptly excreted because of the natriuresis that accompanies SIADH. This concept was hypothetically supported in case 2, in which there was a clear diagnosis of SIADH (as demonstrated with an initial urine Na⁺ level of 189 mmol/l and urine osmolality of 788 mOsmol/kg H₂O associated with only a modest rise in blood Na⁺ (11 mmol/l) with administration of 1.3 litres of 5% saline (1 113 mmol Na⁺ total). Unfortunately urine output data were unavailable for case 2, but from a mathematical standpoint (under the assumption of no water or sodium output) the calculated rise in blood Na⁺ from administration of 1.3 litres 5% saline would have resulted in a substantial (and lethal) blood Na⁺ of 208 mmol/l in this 58 kg woman.

### Table 1. Timeline of progression for fluid intake, signs and symptoms, and laboratory tests for case 2

| Timeline | Pre-race (13 March) | Cycle race (3 hours' riding) | At 55 km/transport | Hospital 1 (16:32, 13 March) | Hospital 2 (17:30, 13 March) | Hospital 2 (14 - 18 March) |
|----------|---------------------|-----------------------------|-------------------|-----------------------------|--------------------------------|-----------------------------|
| Fluid in | 2 500 ml (hypotonic) | 3 750 ml (1.25 l/h water + Coke) | 0 | 1 600 ml Ringer’s lactate (for diagnosis of dehydration) | 100 ml 5% saline (following diagnosis of hyponatraemia) | 1 200 ml 5% saline (100 ml/h for 12 hours until normonatraemic) |
| Signs and symptoms | Tingling of arms and legs Extreme fatigue and nausea Headaches | Numbness (whole body) Sleepiness Vomiting Altered mental status Loss of consciousness Thoughts of dying | AMS Contative and screaming GCS 8/15 | Decorticate movements Papilloedema, bilateral Unresponsive plantar reflexes GCS 3T/15 | | 14 March GCS 3T/15 Papilloedema, bilateral Reaction to pain stimuli 17 March (extubated) Expressive aphasia 18 March (discharged) Short-term memory loss and monosyllabic speech |
| Lab tests and clinical measures | None | | | CT scan: cerebral oedema with opacified right maxillary sinus Serum Na⁺ 124 mmol/l Serum K⁺ 3.6 mmol/l Serum urea 2.7 mmol/l Serum creat 56 µmol/l WBC 16.7×10⁹/l Urine Na⁺ 189 mmol/l Urine osmolality 788 mOsmol/l Urine specific gravity 1.015 Temperature 35.2°C BP 124/89 mmHg Respiration clear, 14/min | 14 March, 06h00 Serum Na⁺ 130 mmol/l Serum K⁺ 4.3 mmol/l Serum urea 2 mmol/l Serum creat 63 µmol/l WBC 12×10⁹/l Temperature 39°C | 14 March, 14h00 Serum Na⁺ 135 mmol/l Diuresis of 300 - 800 ml/h over the next 48 h 17 March Serum Na⁺ 135 mmol/l |
Of curious physiological interest were the discrepancies between water and sodium balance calculations in association with actual blood Na⁺ changes, particularly with regard to case 1, for whom we were able to obtain detailed input and output data from hospital records. These revealed a progressively positive fluid balance associated with the recovery of blood Na⁺ (Fig. 1b). This was curious because we would have expected that a positive fluid balance, commonly associated with dilutional hyponatraemia, would have normalised during recovery with an associated diuresis-induced negative fluid balance, similar to that seen on day 5 (Fig. 1b). This overall positive fluid balance during recovery was unexpected. This suggests that these discrepancies in actual versus measured changes in blood sodium concentration highlight the complexity of fluid and sodium homeostasis, possibly related to osmotic activation and inactivation of sodium stores under non-steady-state conditions. Also unknown were the non-osmotic stimuli to arginine vasopressin secretion, which facilitated fluid retention in these two athletes. Potential non-osmotic stimuli resulting in arginine vasopressin secretion include event stress, heat, plasma volume contraction, ciprofloxacin use (case 1) or many unknown exercise-related stimuli.

In conclusion, female athletes moving relatively slowly and with a history of high fluid intake who present to medical personnel with vomiting and mental status changes should be evaluated promptly for EAH. If symptomatic hyponatraemia is confirmed via a blood test, the recommended treatment is administration of an intravenous dose of hypertonic saline (100 ml 3% or 50 ml 5% saline) to reverse cerebral oedema. Administering Ringer’s lactate to symptomatic athletes without a blood test to rule out or confirm a diagnosis of hyponatraemia should be discouraged, as it can result in a fatal outcome.25

Disclosure. The authors have no conflict or competing interests to disclose.

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Table 2. Comparison of blood and intravenous fluid composition

| Fluid                  | Sodium (Na⁺) (mmol/l) | Chloride (Cl⁻) (mmol/l) | Osmolarity (mOsmol/l) | Other         |
|------------------------|-----------------------|-------------------------|-----------------------|---------------|
| Blood (normal range)   | 135 - 145             | 98 - 108                | 280 - 310             |               |
| Ringer’s lactate       | 130                   | 109                     | 273                   | Isotonic      |
| 0.9% saline            | 154                   | 154                     | 308                   | Isotonic      |
| 3% saline              | 513                   | 513                     | 1 027                 | Hypertonic    |
| 5% saline              | 856                   | 856                     | 1 711                 | Hypertonic    |

Newly risen moon: Wantly in the troubled sky, Bids the coming week.

Haiku: Peter Folb

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