Exercise Associated Hyponatremia

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Disclosures

Outline

- Definition
- Incidence
- Pathophysiology
- Treatment
- Prevention

EAH

- First described in 1985 in a 46 year old female competing in Comrades Marathon (90Km race) from Pietermaritzburg to Durban in South Africa.

EAH

- Initial description was in ultramarathon and ultra endurance events - Ironman distances

- Now has become evident in “shorter” events i.e. marathon distance

EAH

- Strictly defined as serum sodium below laboratory reference range (135 mmol/L) in the period up to 24 hours after prolonged physical activity

Must classify according to symptoms

Biochemical hyponatremia (above 130) is rarely dangerous

EAH

•Symptoms:

Non specific:
Bloating, puffiness, nausea, vomiting, headache

More serious
EAHE – exercise associated hyponatremia with encephalopathy – confusion, disorientation, agitation, delerium
Pulmonary edema, obtundation

EAH

•True incidence is not known as most cases are mild and never measured.

•Reported estimates range from 5-25%

Severe hyponatremia reported in 2% or less

Incidence

Best data is from Almond et al and the 2002 Boston marathon (NEJM 2005:352:1550-56)

Enrolled 766 Runners

488 usable blood samples at the finish line

13% serum Na < 135 mmol/L

0.6% serum Na <120 mmol/L

Almond et al

•Univariate analysis
Hyponatremia was associated with:

Substantial weight gain
Consumption of more than 3L
Consumption of fluid every mile
Racing time >4 hours
Female Gender
Low BMI

Almond et al

•Multivariate Analysis:
Weight Gain

Racing Time (>4 hours versus <3:30)

BMI Extremes

– Female sex, composition of fluids consumed and NSAID use were not correlated

Pathophysiology

2 Main Theories

» Sodium Losses

» Water Gain (in presence of ADH)

Sodium Deficit

– Not borne out in clinical observations

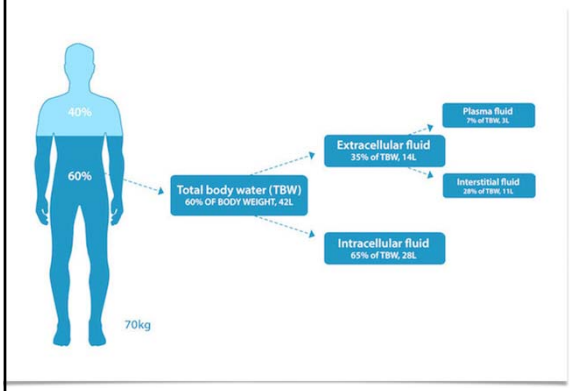
- Prior to 1981 guidelines were not to drink during exercise and no hyponatremia was observed.
- In fact HYPERnatremia post endurance exercise was noted

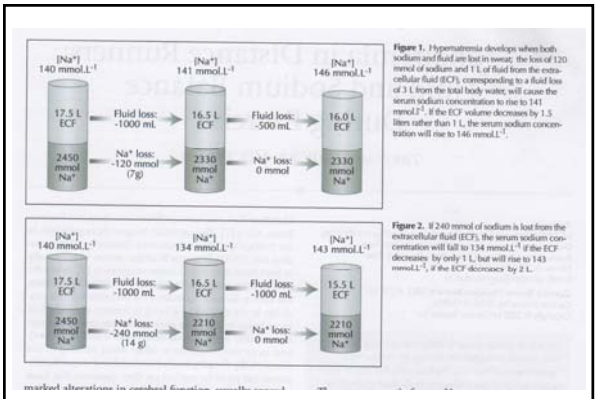
Sodium Deficit

Usual sweat concentration ranges from 10-70 mmol/L

35 mmol/L average, but this varies with body habitus, ambient temperature

Assume that for each litre lost from TBW, 1/3 is from ECF



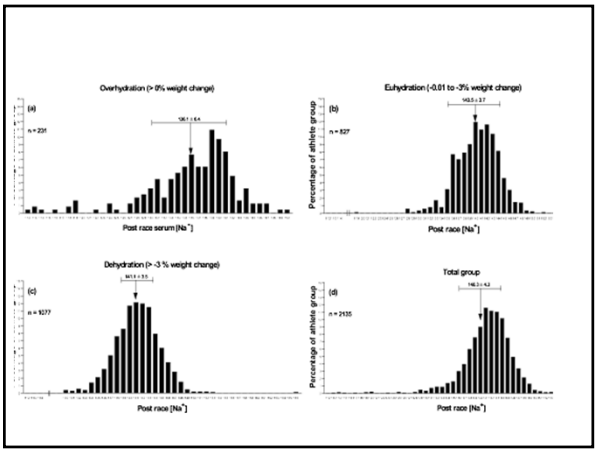


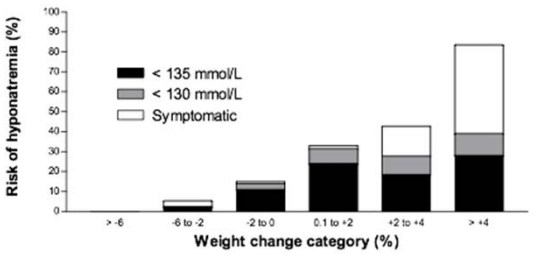
Sodium Deficit

Study of 2135 weighed competitors published in 2005 by Noakes et al.

Linear correlation between weight gain and hyponatremia across running, cycling and ironman events in 4 continents

Some competitors had hyponatremia with volume depletion, but none were clinically significant





Sodium Balance

With body stores of sodium in bone and skin, balance studies have shown that one would need 3 days of complete absence of dietary sodium to begin to approach possible hyponatremia from sodium losses

Non-osmotically active Sodium

Sodium bound to polyanionic proteoglycans in skin, bone and muscle.

Teleologically, body designed to function in sodium poor, potassium rich environment.

Long term balance studies (up to 503 days) have shown storage of sodium without associated fluid retention.

Non-osmotically Active Sodium

There may be some athletes who fail to mobilize these stores or increase movement of Na to the osmotically inactive stores resulting in hyponatremia

If there is a role for sodium loss contributing to EAH, it is negligible

Hydration Status

Recall

» No hyponatremia described prior to 1981 when advice was not to drink during events.

» Change in the advice to athletes resulted in hyponatremia and even death in some cases

Increase Fluid Intake

Why did the advice change during endurance events to drink fluids

Large influence from research done by Gatorade and the Gatorade Sports Science Institute

Gatorade

- "When you sweat, you lose more than water. You also lose critical electrolytes, like sodium and potassium, which help the brain communicate with muscles and regulate fluid level balance throughout the body. Significant losses in fluids and electrolytes can negatively impact performance, especially during long bouts of training".

250mg Na =11mmol therefore 18mmol/L

Athletic Performance and Fluid Status

Meta-analysis from Goblet et al published in British Journal of Sports Medicine in 2011

5 Studies looking at cycling time trial performance in 39 subjects

Power output increased slightly with 'dehydration' of 2%

Athletic Performance and Fluid Status

Using a random effects model Goulet showed a BW loss of 2.2% resulted in a mean power increase of 0.06%

Some studies did show a decrement in performance, but only when athletes were not permitted to drink and postulate that sensation of thirst impaired performance

Athletic Performance and Thirst

Drinking according to command of thirst was associated with an increase in power compared to drinking below and above the command of thirst

End of exercise BW loss correlated well with drinking commands 2.8% vs 1.6% vs 0.6%

Athletic Performance and BW

Haille Gebresalassie - 2008 Marathon world record setter (2:03:59)

» lost 10% of his body weight en route to establishing that time

» (current world record is 2:02:57 Dennis Kimetto)

Athletic Performance and BW

Noakes et al studied body weight changes in relation to finishing times at the St. Michel Marathon in France 2009, published in the British Journal of Sports Medicine 2011

Inverse relationship between finishing time and weight loss.

Avg weight loss >3Kg in those finishing under 3hours

Over hydration

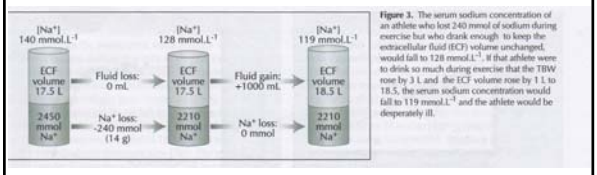
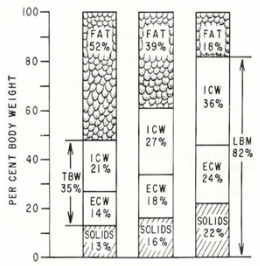


Figure 3. The serum sodium concentration of an athlete who lost 240 mmol of sodium during exercise but who drank enough to keep the extracellular fluid (ECF) volume unchanged, would fall to 128 mmol.L^{-1}. If that athlete were to drink so much during exercise that the TBW rose by 3 L and the ECF volume rose by 1 L to 18.5, the serum sodium concentration would fall to 119 mmol.L^{-1} and the athlete would be desperately ill.

Total Body Water

- Water accounts for 50-70% of body weight
- Average is ~60%
- Percentage varies with:
  - gender, age
  - adipose tissue content
- Water content correlates inversely with body fat stores
  - thin men have the highest percentage of water
  - obese women have the lowest percentage of water



Total Body Water = 0.7LBM + 0.1AT

where LBM = lean body mass (in kg) and AT = adipose tissue (in kg) 6

Metabolic Water

Metabolism of glycogen can produce water but it is small

Treadmill exercise at 70% max capacity

» 144g/h of glycogen metabolized

» Sweat rate was 1200ml/hr

» Swart et al. Nephron Physiology. 2011;118;45-51

Over hydration

How is it possible to over hydrate?

Normal renal response is merely to excrete the excess free water

Renal capacity to excrete free water is in the order of 1000ml/hr

Assume sweat losses during exercise of 500ml/hr

Need to drink >1500ml/hr to over hydrate

Renal blood flow in exercise

Decrease in renal blood flow correlates with intensity of exercise

Normal response is to decrease free water excretion and decrease sodium excretion

Likely in response to catecholamines and ADH production

NSAIDS

Early literature suggested that NSAIDs play a role in development of EAH

In the study from Almond et al NSAIDs were not relevant in the multivariate analysis

There is an effect on renal blood flow limiting free water excretion

NSAIDS

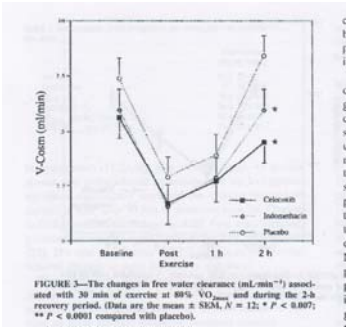
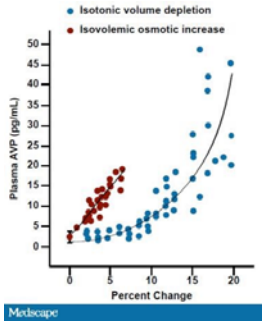


FIGURE 3—The changes in free water clearance (mL·min⁻¹) associated with 30 min of exercise at 80% VO_{2max} and during the 2-h recovery period. (Data are the mean ± SEM, $N = 12$; * $P < 0.007$; ** $P < 0.0001$ compared with placebo).

Water Plus ADH required to develop hyponatremia

ADH



ADH

Siegel at al in the Clinical Journal of Sports Med 2005

» 22 collapsed runners with EAH

» 43% had detectable levels of ADH despite hypo-osmolarity

» 2 runners with fatal cerebral edema had Uosm >100 mOsm/Kg

Non-Osmotic ADH

Hew-Butler et al British Journal of Sports Med 2010. 44:594-597

» Observational Study of 33 cyclists in 109KM race

» Pre and post race: body weight, blood and urine samples

» 4 fold increase in ADH levels despite 2mmol/L decrease in plasma Na

Non-Osmotic ADH

Urine indices correlated well with ADH levels indicated a normal renal response to ADH during exercise

Plasma volume was not correlated to ADH levels suggesting that plasma volume was not the primary non-osmotic stimulus.

Degree of plasma volume depletion (4%) should not have been enough to cause the ADH stimulation

Non-Osmotic ADH

Same group also looked at runners participating in a 56 Km ultra-marathon

82 runners

Ad lib fluid consumption

Plasma Na unchanged pre to post race

Body weight -3.8%

Plasma Volume -5.8%

ADH levels were 4 times higher post race to pre race

Non-Osmotic ADH

Also found elevated oxytocin, cortisol and IL-6 and proBNP levels

Mathematical modelling from this group has shown influence of IL-6 and oxytocin as predictors of ADH response

Non-Osmotic ADH

Muscle damage and rhabdomyolysis also implicated but not sufficient

Higher CK levels after running, but elevated ADH levels also seen after cycling with little change in CK levels

Non-Osmotic ADH

Active muscles produce IL-6 during prolonged exercise

» Degrees of production seems to correlate with duration and intensity of exercise

» 12 fold after 56 Km foot race, to 8000 fold during 245 Km mountain run

» May have physiologic role in lipolysis

Causes of EAH

? Small component of Na losses through sweat

Decreased renal free water excretion from ADH - Mainly non-osmotically stimulated release

Fluid Consumption

Does the type of Fluid Matter

Can sports drinks really prevent EAH

» Na content of most sports drinks is in the order or 10-20 mmol/L so they are markedly hypotonic

» No data to support that Na supplementation is useful in EAH

Sodium Supplementation

Hoffman et al 2015 in Medicine in Science and Sports

161 KM Western States Endurance Run

The only correlation to hyponatremia was change in body mass

Those gaining weight had lowest serum Na

» Type and amount of sodium ingested did not affect serum Na

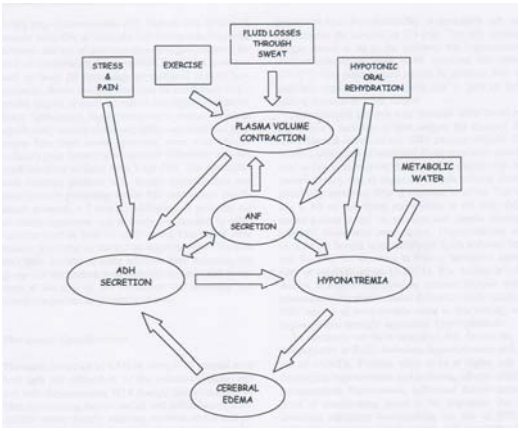
Sodium Supplementation

Study was not perfect.

Self reporting on type and amount of sodium supplement taken

Runners were pretty meticulous in their preparation and reliable

Most runners had bilk of their supplemental sodium near the end of the race



Treatment

Symptom Driven

» Mild, asymptomatic hyponatremia

» Fluid restriction and observation until spontaneous diuresis occurs

» Resist the urge to offer fluids .

» Often athletes have retained fluids in GI tract which they will absorb over time.

» Caution with NS. This can worsen symptoms.

Treatment

Monitor urine output and osmolarity to assess for free water excretion.

All reported cases of death occurred with NS infusion.

Ensure NS is reserved only if clinically volume depleted

Treatment

Severe or symptomatic hyponatremia
» Hypertonic saline

» No evidence of CPM in athletes with EAH corrected with hypertonic saline

Treatment

Ayus et al Annals of Internal Medicine 200

» Seven patients who completed marathons between 1993-1999
» All patients admitted with neurologic symptoms and non-cariogenic pulmonary edema

Treatment

» 6/7 patients received hypertonic saline.
» Na rose by 10 points over 12 hours
» These 6 had full recovery.
» 1/7 did not receive 3% saline and died

Treatment

» Initial CT heads confirmed cerebral edema in all of the patients

» Follow up MRI in 5/6 patients at one year were normal with no sequelae noted

Treatment

Suggested dose in the field is 100 cc of 3%
» 2-3 mmol increase in serum Na with this
» Slightly higher than expected rise in serum Na likely from decrease ADH
» Stop when water diuresis occurs

Treatment

Loop Diuretics
» Consider when severely volume overloaded or
» Urine Osmolarity is is elevated (elevated urine Na or K)

Treatment

Newer agents not studied well in this field

» Vasopressin Receptor Antagonists

» Aquaretics

» Tolvaptan, Conivaptan

Caution with correction of hypokalemia as this will result in shifts and increases in serum Na

Prevention

Two main factors required

ADH

Hypotonic Fluids

As yet we have no mechanism to turn off ADH in exercise

Limit consumption of fluids

Prevention

Limit hydration stations at races to every 5Km

Advice to runners to only drink when thirsty

No need to replace all fluid lost during a race

Prevention

Education to athletes needs to be changed

» 1996 guidelines were to drink sports drinks and as much as possible

» American College of Sports Medicine

» Only platinum sponsors of ACSM are Gatorade and the GSSI

Prevention

Current IOC guidelines still recommend replacing fluids to maintain same body weight before and after exercise, but this is dangerous

Remember there have been NO reported deaths from HYPERnatremia

Summary

EAH occurs in small number of athletes

Usually mild and “sub-clinical”

Serious cases are reported with potentially devastating consequences

Pathophysiology is from ADH plus water - not dissimilar to any cause of hyponatremia

Cause for exercise induced increase in ADH is not 100% clear

Summary

It is a preventable condition

» Drink to thirst

» Limit availability of fluids on race courses

» Correct advice to athletes

Summary

Treatment

» Prompt recognition

» Avoid urge to give NS

» Await for spontaneous aquaresis

» Consider furosemide

» Hypertonic saline if severe