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ORIGINAL ARTICLE

Fluid intake and changes in limb volumes in male ultra-marathoners: does fluid overload lead to peripheral oedema?

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Abstract An increase in body mass due to oedema has been previously described. The aim of this study was to investigate a potential association between both fluid and electrolyte intake and the formation of peripheral oedemas. Fluid and electrolyte intakes and the changes in limb volumes in 50 male 100-km ultra-marathoners were measured. Pre- and post-race serum sodium concentration ($[Na^+]$), serum aldosterone concentration, serum copeptin concentration, serum and urine osmolality and body mass were determined. Fluid intake, renal function parameters and urinary output, as well as the changes of volume in the extremities, were measured. The changes of volume in the limbs were measured using plethysmography. Serum $[Na^+]$ increased by 1.6%; body mass decreased by 1.9 kg. Serum copeptin and aldosterone concentrations were increased. The change in serum copeptin concentration and the change in serum $[Na^+]$ correlated positively; the change in serum $[Na^+]$ and body mass correlated negatively. A mean fluid intake of 0.58 L/h was positively related to running speed and negatively to post-race serum $[Na^+]$. Total fluid intake was positively related to the changes in both arm and lower leg volumes. Running speed was positively associated with the changes in arm and lower leg volumes; race time was related to the changes in serum copeptin or aldosterone concentrations. To conclude, fluid intake was related to the changes in limb volumes, where athletes with an increased fluid intake developed an increase in limb volumes.

Keywords Electrolytes · Aldosterone · Vasopressin · Ultra-endurance · Hyponatremia

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Introduction

Exercise-associated hyponatremia (EAH) is a common and severe electrolyte disorder in endurance athletes (Noakes et al. 1990; Siegel et al. 2007; Speedy et al. 1999). EAH was first described in the scientific literature in ultra-runners in South Africa by Noakes et al. (1985) as serum or plasma sodium concentration ($[Na^+]$) <135 mmol/L during or within 24 h post-race (Hew-Butler et al. 2005, 2008; Kipps et al. 2011; Rosner and Kirven 2007; Siegel et al. 2007; Speedy et al. 1999). Athletes with EAH may present symptoms, such as weakness, confusion, headache, nausea or vomiting, increasing to complications such as encephalopathy, seizures, pulmonary oedema, cerebral oedema and death (Ayus et al. 2000; Hew-Butler et al. 2005; Speedy et al. 2001). Alternatively, athletes with serum $[Na^+]$ levels <135 mmol/L may be asymptomatic (Hew-Butler et al. 2005, 2008; Knechtle et al. 2011a, b; Rosner and Kirven 2007).

In runners, the prevalence of EAH varies widely from 0.3% in a 90-km race (Noakes et al. 1990) over 3% at the 2006 'Zurich Marathon' (Mettler et al. 2008) to 12.5% in the 2003 'London Marathon' (Kipps et al. 2011) and 13% in the 2002 'Boston Marathon' (Almond et al. 2005). In ultra-endurance athletes such as Ironman triathletes, a prevalence of 18% EAH has been reported at the 1997

'New Zealand Ironman' (Speedy et al. 1999). These prevalence rates of EAH were rather low considering a very recent study on ultra-marathoners where Lebus et al. (2010) reported, at the 'Rio Del Lago 161 km endurance run' in 2008, an extremely high prevalence of EAH of 51.2%. In another ultra-marathon over 24 h, however, no case of EAH was found (Knechtle et al. 2010a). In general, prevalence of EAH was no higher in ultra-endurance athletes (Knechtle et al. 2011a, b) when compared with existing reports on marathoners and Ironman triathletes.

The reason of developing EAH is a behavioural condition such as overdrinking during an endurance performance (Noakes et al. 2005; Noakes 2011). Studies showed that when athletes were encouraged to limit their fluid intakes, drinking only in response to thirst, there were no cases of EAH (Noakes et al. 2004; Speedy et al. 2000b). The difference in prevalence of EAH such as an increasing number of cases of EAH in the United States (Lebus et al. 2010) as compared to a decreasing number of cases in South Africa and in New Zealand (Noakes et al. 2005) as well as in Europe (Knechtle et al. 2010a, 2011a, b) can be explained by the fact that the sports drink industry could promote in America its erroneous 'science of hydration' so that athletes were overdrinking during an endurance performance (Noakes 2010, 2011). In contrast to America, South Africa and New Zealand did not spread the wrong message about 'science of hydration', in these parts of the world the scientist were able to spread the true message across so athletes began to drink in accordance with the dictates of thirst during exercise (Noakes 2010, 2011). However, in the 161-km ultra-marathon from Lebus et al. (2010), the runners lost 2.9% in body mass and 16.4% in fat mass although 51.2% of the finishers developed EAH. Nine finishers (22%) with post-race serum $[Na^+]$ <135 mmol/L lost 3.5–8% in body mass and where therefore not likely to be overhydrated. These findings were in contrast to other studies that found EAH to be relatively rare in subjects who lost >3% in body mass. Presumably, the loss in body mass was associated with the loss in fat mass as it has already been shown in ultra-marathoners (Knechtle et al. 2011d).

Fluid overload can largely account for the development of EAH, and a correlation between an increase in body weight due to fluid overload and a decrease of serum $[Na^+]$ was described in several studies (Irving et al. 1991; Mettler et al. 2008; Noakes et al. 2005; Speedy et al. 1999). We know that this form of behaviour is the only risk factor for EAH since when athletes are told to drink for thirst during exercise the incidence of EAH becomes negligible as described in races held in South Africa and New Zealand. In Ironman triathletes, large changes in body weight during a triathlon were not associated with a greater prevalence of medical complications or higher rectal temperatures but were associated with higher serum $[Na^+]$ (Sharwood et al. 2004). In another study on Ironman triathletes, there was a significant and positive correlation between serum $[Na^+]$ and body weight change during the race: the greater the body weight loss, the higher the serum $[Na^+]$ (Speedy et al. 1997b). An inverse relationship between post-race serum $[Na^+]$ and change in body weight was observed in a further study on Ironman triathletes (Speedy et al. 1997a). This finding has been confirmed in laboratory studies (Noakes 2011).

An increase in body mass during endurance performance might also be due to a development of oedema. Williams et al. (1997) and Milledge et al. (1982) investigated the effect of a 5–7 days hill walk, including the post-exercise days, on fluid homeostasis. During their investigation, the athletes were allowed to drink water ad libitum. Williams et al. (1997), as well as Milledge et al. (1982) described a positive water balance with a net movement of fluid from the intracellular to the extracellular space and, therefore, an expansion of the extracellular space. Furthermore, they found that the packed cell volume concentrated, indicating a decrease of the volume of the vascular compartment. The expansion of the extracellular volume was supposed to lead an increase in leg volume (Milledge et al. 1982) and visible facial and ankle oedemas might appear (Williams et al. 1997).

The development of oedemas after an ultra-endurance performance such as a Triple Iron ultra-triathlon was also recently described in a case report by Knechtle et al. (2009a). These authors presumed that oedemas developed in the skeletal muscle. The oedemas of the lower limbs were clinically visible starting on day 2 post-race and disappearing on day 6 post-race. Different mechanism apart from fluid overload could lead to a retention in total body water in ultra-endurance athletes such as protein catabolism with the development of hypoproteinemic oedemas (Lehmann et al. 1995), an increased protein synthesis leading to increased plasma volume (Maughan et al. 1985; Mischler et al. 2003), an increased $[Na^+]$ retention (Fellmann et al. 1999) due to an increased activity of aldosterone (Wade et al. 1981) or dehydration and an impaired renal function due to skeletal muscle damage (Uberoi et al. 1991).

The aim of the present study was to investigate a potential association between both fluid and electrolyte intake and the formation of peripheral oedemas leading to an increase in limb volumes. Since a long race duration (Almond et al. 2005; Chorley et al. 2007; Hew et al. 2003; Noakes et al. 1985) and an increased availability of beverages (Hew-Butler et al. 2005; Speedy et al. 2000b) are described to increase the risk for fluid overload, we investigated the development of peripheral oedemas in a 100-km ultra-marathoners. In these races, running speed is

usually low (Knechtle et al. 2009b, 2010b, c, 2011c) and the athletes can ingest fluids at several aid stations as well as being provided by their support crews (Knechtle et al. 2009b, 2010b). We hypothesised that (i) the increased availability of fluids would lead to fluid overload, thus leading to an increased prevalence of EAH and (ii) that an increased fluid intake during a race would lead to oedemas of the extremities with an increase in limb volumes.

Methods

Subjects

The organiser of the '100-km Lauf Biel' (http://www.100km.ch) in Biel, Switzerland, contacted all participants of the 2010 race 3 months before the start via a separate newsletter and informed them about the planned investigation. Fifty-six recreational male ultra-runners volunteered to participate in the study, 50 participants finished the race successfully within the time limit of 21 h. The characteristics of both their anthropometry and training are represented in Table 1. The study was approved by the Institutional Review Board for the Use of Human Subjects of the Canton of Zurich, Switzerland, and all athletes gave their informed written consent. The '100-km Lauf Biel' has a long tradition in Switzerland (Knechtle et al. 2009b, 2010b, c, 2011b, c). The race has no sponsor for sports nutrition and the race director gives no special advices regarding hydration strategy for the race (http://www.100km.ch).

The race

The race took place on June 11, 2010. The athletes started the 100-km road course ultra-marathon at 10:00 p.m. During these 100 km, with a total change in altitude of ~645 m, the organiser provided a total of 17 aid stations offering an abundant variety of food and beverages such as hypotonic sports drinks, tea, soup, caffeinated drinks, water, bananas, oranges, energy bars and bread. The athletes were allowed to be supported by a cyclist to have additional food and clothing, if necessary. The temperature at the start was 21.7°C, dropping to 15.6°C during the night and rising to 18.1°C the next day. Humidity was 52% at the start, rising to 62% during the night and to 69% the next day.

Table 1 Characteristics of the subjects ($n = 50$)

	n	Mean	CI 95%
Age (years)	50	47.8	(45.4; 50.3)
Body height (m)	50	1.79	(1.77; 1.81)
Body mass (kg)	50	74.9	(72.2; 77.7)
Body mass index (kg/m^2)	50	23.3	(22.6; 23.9)
Experience in endurance sports (years)	50	11.8	(9.6; 14.1)
Training volume (h/week)	50	8.6	(5.6; 11.7)
Training volume (km/week)	50	66.5	(58.7; 74.4)
Training speed (km/h)	50	10.7	(10.3; 11.1)
Marathons finished (number)	50	33	(17.4; 48.7)
100 km races finished (number)	50	3.9	(2.4; 5.4)
Personal best marathon time (h:min)	48	03:31	(03:22; 03:40)
Personal best 100 km time (h:min)	35	11:22	(10:41; 12:03)

Results are presented as mean and 95% CI

Measurements and calculations

On June 11, 2010 between 05:00 p.m. and 10.00 p.m., the pre-race measurements were performed. Body mass was measured using a commercial scale (Beurer BF 15, Beurer GmbH, Ulm, Germany) to the nearest 0.1 kg after voiding of the urinary bladder. Urine samples were collected and venous blood samples were drawn. Two Sarstedt S-Monovettes (serum gel, 7.5 ml) for chemical and one Sarstedt S-Monovette (EDTA, 2.7 ml) (Sarstedt, Nümbrecht) for heamatological analysis were drawn. Monovettes for serum and plasma were centrifuged at 3,000g for 10 min at 4°C. Plasma was collected and stored on ice. Urine was collected in Sarstedt monovettes for urine (10 ml). Blood and urine samples were transported immediately after collection to the laboratory and were analysed within 6 h.

In the venous blood samples, haemoglobin, haematocrit, serum sodium concentration ($[Na^+]$), serum potassium concentration ($[K^+]$), serum creatinine concentration, serum urea concentration, and serum osmolality were measured. Haematologic parameters were determined using ADVIA® 120 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Serum parameters were measured using COBAS INTEGRA® 800 (Roche, Mannheim, Germany). Osmolality of serum and urine samples was determined using Fiske® Modell 210 Mikro-Osmometer (IG Instrumenten-Gesellschaft AG, Zurich, Switzerland). Serum aldosterone concentration was measured using RIA (Radio Immuno Assay) with Gamma-Counter 1277 (DRG Instruments GmbH, Germany). Serum copeptin concentration was analysed using TRACE (Time Resolved Amplified Kryptat Emssion) with Kryptor (BRAHMS GmbH, Germany). In the urine samples, creatinine, urea, $[Na^+]$, $[K^+]$, urine specific gravity and urine osmolality were determined. Urine specific gravity was analysed using Clinitek Atlas® Automated Urine Chemistry Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Creatinine and urea were measured using COBAS INTEGRA® 800. Electrolytes were determined using ISE IL 943 Flame Photometer (GMI, Inc., Ramsey, MN, USA).

We expressed the urine concentrations as fractional excretions. This applied to the following parameters:

sodium, potassium, urea, and osmolality. We used the general formula: fractional excretion of parameter = [(parameter$_{urine}$ × creatinine$_{serum}$)/(parameter$_{serum}$ × creatinine$_{urine}$)] × 100 following Espinel (1976). Transtubular potassium gradient was calculated using the equation: transtubular potassium gradient = (potassium$_{urine}$ × osmolality$_{serum}$)/(potassium$_{serum}$ × osmolality$_{urine}$) according to West et al. (1986). Percentile change in plasma volume was determined following Strauss et al. (1951).

The volume and the changes of volume in the arm and lower leg were measured using the principle of plethysmography. We constructed a vessel using Plexiglas® with the internal dimensions of 386 mm length and 234 mm width. These dimensions were chosen so that any foot size of a male runner would fit in the vessel. The vessel was then filled to 450 mm with plain water and the limb was immersed. For the lower limb, the upper limit of the water was at the middle of the knee; for the upper limb, the upper limit of the water was at the armpit after immersion. The water level was then measured to the nearest 1 mm and the corresponding volume calculated using the length, width and height in millimetres of the displaced water and defined as the volume of the arm and lower leg, respectively. Cubic millimetres were then converted to litres.

The thickness of subcutaneous adipose tissue was measured at six sites to the nearest 0.1 mm using a LIPOMETER® as described by Jürimäe et al. (2007). In order to detect an increase in the thickness of the subcutaneous adipose tissue due to a clinically visible or palpable oedema in the face and limbs, the thickness of subcutaneous adipose tissue at the right side of the body at *arcus zygomaticus*, the middle of *os metacarpale III*, at the *margo medialis tibiae*, one handbreadth above *malleolus medialis*, directly at *malleolus medialis* and at *os cuneiforme mediale* was measured. The athletes were asked for their subjective feelings regarding the swelling of their hands and feet using a subjective 0–10 scale, where 0 was defined as 'I feel no swelling in hands or feet' and 10 as 'I feel an extreme swelling in hands and feet'. Between 0 and 10, no other labels beside the extremes were given.

Immediately after arrival at the finish line, the identical measurements were repeated. Between the pre-race and post-race measurements, the athletes recorded their intake of food and drinks using a prepared paper and pencil. At each aid station they noted both the kind and the amount of ingested food and fluids. At these aid stations, liquids and food were prepared in a standardised manner, i.e., beverages and food were provided in standardised size portions. The drinking cups were filled to 0.2 L; the energy bars and the fruits were halved. The athletes also recorded additional food and fluid intake provided by their support crew, as well as their intake of salt tablets and other supplements. The compositions of fluids and solid food were estimated using a food table (Kirchhoff 2002). The day before the race, during the race and the 3 days after the race, the athletes recorded their urinary output using a graduated jug to the nearest 0.1 L.

Statistical analysis

Data are presented as mean values and 95% confidence interval (CI). Pre- and post-race results were compared using paired *t* test. Pearson correlation analysis was used to check for associations between the measured and calculated parameters. Statistical significance was accepted with $p < 0.05$ (two-sided hypothesis).

Results

Fifty of the 56 subjects finished the race within 12:15 (11:51; 12:47) h:min, running at a mean speed of 8.4 (8.0; 8.7) km/h. Their training and pre-race experience is represented in Table 1. The weekly running kilometres ($r = -0.28$, $p = 0.047$), the speed in running during training ($r = -0.58$, $p < 0.0001$) and the personal best marathon time ($r = 0.61$, $p < 0.0001$) were related to the 100-km race time.

Table 2 shows the pre- and post-race measurements and their changes. Body mass decreased by 1.9 kg (2.5%) ($p < 0.0001$). The volume in both the lower leg and the arm showed no changes. In detail: in 19 runners arm the volume increased, in 20 runners the volume showed no change and in 11 runners arm the volume decreased. The leg volume increased in 11 runners, remained stable in 13 runners, and decreased in 26 runners. The thickness of subcutaneous adipose tissue increased at *os metacarpale III* ($p < 0.0001$), at *malleolus medialis* ($p < 0.001$) and at *os cuneiforme mediale* ($p = 0.0332$). The subjective feeling of swelling increased for both the hands ($p = 0.0002$) and the feet ($p < 0.0001$).

Serum copeptin and aldosterone concentrations increased ($p < 0.0001$). Haemoglobin and haematocrit remained unchanged, calculated plasma volume increased by 1.0 (7.8)% ($p > 0.05$). Serum osmolality increased by 1.9% ($p < 0.0001$). Serum [Na^+] increased by 1.6% ($p < 0.0001$), serum [K^+] remained unchanged. Serum urea concentration increased ($p < 0.0001$). In 2 of the 50 successful finishers, serum [Na^+] was both pre- and post-race <135 mmol/L. In one subject, serum [Na^+] dropped from 133 mmol/L pre-race to 132 mmol/L post-race; in the other subject, serum [Na^+] increased from 131 mmol/L pre-race to 133 mmol/L post-race. The change in body mass was significantly and negatively related to both post-race serum [Na^+] and running speed (see Fig. 1).

Table 2 Results of the physical, haematological and urinary parameters before and after the race

	Pre-race*	Post-race*	Percental change*	*p* value**
Body mass (kg)	74.9 (72.2; 77.7)	73.0 (70.3; 75.7)	−2.5 (−3.1; −2.1)	<0.0001
Volume of the lower leg (L)	2.36 (2.25; 2.47)	2.38 (2.26; 2.49)	0.86 (−1.85; 3.58)	0.57
Volume of the arm (L)	4.08 (3.94; 4.23)	4.05 (3.89; 4.20)	−0.65 (−3.21; 1.96)	0.45
Thickness subcutaneous fat at *arcus zygomaticus* (mm)	3.20 (2.84; 3.55)	3.14 (2.79; 3.49)	2.58 (−7.74;12.91)	0.63
Thickness subcutaneous fat at *os metacarpale III* (mm)	2.23 (1.84; 2.61)	4.38 (3.80; 4.96)	165.58 (99.34; 231.82)	<0.0001
Thickness subcutaneous fat at *margo medialis tibiae* (mm)	3.27 (2.85; 3.68)	3.59 (3.29; 3.89)	24.45 (10.01; 40.89)	0.07
Thickness subcutaneous fat at *malleolus medialis* (mm)	2.10 (1.86; 2.34)	3.30 (2.94; 3.66)	80.53 (50.56; 110.51)	<0.0001
Thickness subcutaneous fat at *os cuneiforme mediale* (mm)	1.75 (1.61; 1.88)	2.03 (1.79; 2.27)	23.28 (4.57; 41.99)	0.03
Subjective feeling of swelling of the hands	1.0 (0.6; 1.4)	2.9 (2.0; 3.8)		0.0002
Subjective feeling of swelling of the feet	0.9 (0.5; 1.3)	2.8 (2.0; 3.6)		<0.0001
Plasma copeptin concentration (pmol/L)	6.4 (5.5; 7.4)	75.0 (50.4; 99.6)	1,212 (795; 1,628)	<0.0001
Plasma aldosterone concentration (ng/L)	90 (79; 102)	424 (351; 496)	454 (333; 575)	<0.0001
Haemoglobin (g/dl)	14.5 (14.3; 14.8)	14.5 (14.2; 14.8)	−0.4 (−1.6; 0.9)	0.51
Haematocrit (%)	43.5 (42.7; 44.2)	43.3 (42.5; 44.2)	0.3 (−1.6; 1.0)	0.57
Serum sodium concentration (mmol/L)	136.6 (135.4; 136.7)	138.2 (137.6; 138.9)	1.6 (1.0; 2.2)	<0.0001
Serum potassium concentration (mmol/L)	4.1 (4.0; 4.2)	4.3 (4.2; 4.4)	3.9 (0.1; 7.7)	0.07
Serum glucose concentration (mmol/L)	5.3 (5.0; 5.6)	5.4 (5.1; 5.8)	7.1 (−1.8; 16.1)	0.47
Serum creatinine concentration (μmol/L)	77.8 (74.5; 81.1)	100.4 (93.3; 107.5)	30.1 (21.1; 39.2)	<0.0001
Serum urea concentration (mmol/L)	5.7 (5.4; 6.0)	9.1 (8.4; 9.8)	61.5 (49.5; 73.6)	<0.0001
Serum osmolality (mosmol/kg H_2O)	296.4 (295.1; 297.6)	302.0 (299.9; 304.1)	1.9 (1.2; 2.7)	<0.0001
Urinary specific gravity (g/ml)	1.017 (1.015; 1.019)	1.026 (1.015; 1.028)	0.93 (0.72; 1.1)	<0.0001
Urinary osmolality (mosmol/kg H_2O)	672.0 (531.0; 773.0)	893.5 (831.0; 955.0)	157.5 (86.0; 224.0)	<0.0001
Fractional potassium excretion (%)	0.114 (0.098; 0.129)	0.191 (0.168; 0.214)	100 (64; 136)	<0.0001
Fractional urea excretion (%)	52.7 (49.1; 56.4)	31.0 (26.8; 35.1)	−39.0 (−47.7; −30.2)	<0.0001
Transtubular potassium gradient (ratio)	28.3 (21.8; 34.8)	99.7 (84.9; 114.6)	828 (378; 1,278)	<0.0001

* $n = 50$, mean value, CI 95%, ** by paired *t* test

Fractional sodium excretion decreased, fractional potassium excretion increased, fractional urea excretion decreased, fractional osmolar excretion decreased and transtubular potassium gradient increased ($p < 0.001$).The athletes consumed a total of 7.3 (6.6; 7.9) L of fluids during the race, equal to 0.58 (0.53; 0.63) L/h. Expressed as a rate, the athletes consumed 7.9 (6.4; 9.4) ml kg^{-1} h^{-1}. Regarding the intake of electrolytes, they ingested 7.1 (5.6; 8.6) mg of sodium h^{-1} kg^{-1} and 2.4 (2.1; 2.8) mg of potassium h^{-1} kg^{-1}. Sodium intake was neither related to post-race serum [Na^+] nor to the change in serum [Na^+] ($p > 0.05$). Sodium intake showed no association with both the change in lower leg volume ($r = 0.10$, $p = 0.49$) and the change in arm volume ($r = 0.24$, $p = 0.088$). Energy intake was 3.2 (2.6; 3.9) kcal h^{-1} kg^{-1}.

Fluid intake was not associated with post-race serum copeptin concentration, or the change in serum copeptin concentration ($p > 0.05$). Also, fluid intake correlated neither to post race serum aldosterone concentration nor to the change in serum aldosterone concentration ($p > 0.05$). The hourly fluid intake was significantly and positively related to the running speed (see Fig. 1) with faster athletes drinking more fluids while running. Fluid intake was significantly and negatively related to the post-race serum [Na^+] (see Fig. 1) and significantly and negatively to the change in serum [Na^+] ($r = -0.38$, $p = 0.0072$). Although the volumes in arm and lower leg showed no changes during the race, total fluid intake during the race was related to the change in both the arm and the lower leg volume (see Fig. 2). Running speed was associated with the changes in both arm volume lower leg volume (see Fig. 2). Table 3 shows the relationship between fluid intake and the changes in the thickness of subcutaneous adipose tissue. The changes in the thicknesses of subcutaneous adipose tissue at *mallelous medialis* and at *os cuneiforme mediale* were not associated with the changes in lower leg volume; the changes in the thicknesses of subcutaneous adipose tissue at the middle of *os metacarpale III* also showed no relationship with the changes in arm volume ($p > 0.05$).

The change in plasma volume was associated with total fluid intake ($r = 0.30$, $p = 0.0357$), the changes in serum

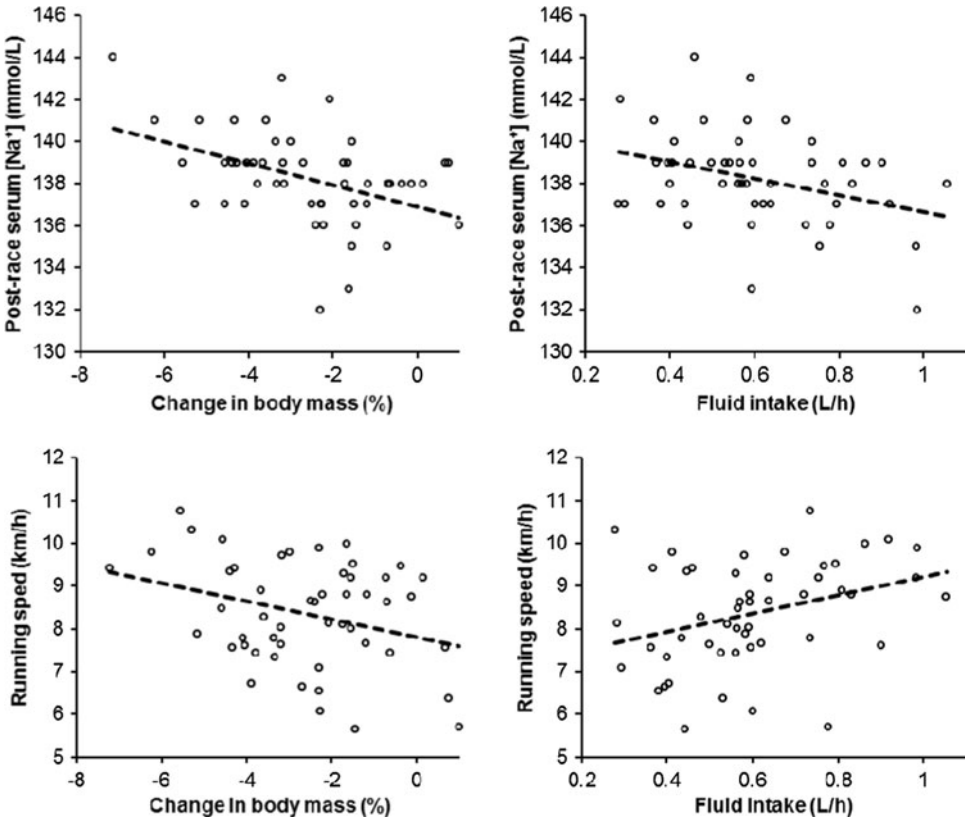

Fig. 1 The change in body mass was significantly and negatively related to post-race serum [Na^+] ($r = -0.42$, $p = 0.0022$) and to running speed ($r = -0.31$, $p = 0.027$). Hourly fluid intake was significantly and negatively related to post-race serum [Na^+] ($r = -0.34$, $p = 0.0145$), and significantly and positively to running speed ($r = 0.33$, $p = 0.0182$) ($n = 50$)

osmolality ($r = -0.32$, $p = 0.0241$), the changes in serum aldosterone concentration ($r = -0.40$, $p = 0.0037$), the changes in lower leg volume and the changes in arm volume (see Table 3), but showed no association with the changes in serum copeptin concentration, fractional urea excretion, sodium intake, or the changes in the thicknesses of subcutaneous fat at *os metacarpale III*, at *malleolus medialis* or at *os cuneiforme mediale* ($p > 0.05$). The increase in serum osmolality was highly significantly associated with the increase in both serum urea ($r = 0.71$, $p < 0.0001$) and serum [Na^+] ($r = 0.51$, $p < 0.0001$). For urine, the increase in osmolality was highly significantly related to the increase in urine urea ($r = 0.77$, $p < 0.0001$) and to the decrease in urine [Na^+] ($r = 0.57$, $p < 0.0001$). There was a strong and positive relationship between the changes in serum osmolality and serum copeptin concentration ($r = 0.61$, $p < 0.001$) and between serum copeptin concentration and urine osmolality ($r = 0.38$, $p < 0.001$). The changes in serum copeptin concentration were related to the changes in serum [Na^+] ($r = 0.36$, $p = 0.01$); post-race serum copeptin concentration was not associated with post-race serum [Na^+]. Post-race serum copeptin concentration and the change in serum copeptin concentration were not related to running speed. The changes in serum aldosterone concentration were highly significantly and positively associated with the post-race changes in the transtubular potassium gradient ($r = 0.37$, $p = 0.0078$). Post-race serum aldosterone concentration ($r = 0.36$, $p = 0.0110$) and the change in serum aldosterone concentration ($r = 0.38$, $p = 0.0065$) were both significantly and positively related to running speed. Post-race serum aldosterone concentration was not related to post-race serum [Na^+].

The athletes recorded 5.6 (4.5; 6.6) micturitions and voided 1.5 (1.2; 1.8) L of urine during the race, equal to 1.6 (1.3) ml h^{-1} kg^{-1}. Urine excretion increased significantly during the race, as compared to pre-race, and was reduced post-race, reaching pre-race levels only on day 3 after the race. The changes in serum copeptin concentration were neither related to the number of micturitions nor to urine excretion during the race ($p > 0.05$). The change in the subjective feeling of swelling in the hands was not associated with the change in the thickness of subcutaneous fat at *os metacarpale III*; or the feet at *malleolus medialis*, or at *os cuneiforme mediale* ($p > 0.05$). Also, the change in the subjective feeling of swelling in the hands showed neither an association with the change in arm volume or with the change in leg volume ($p > 0.05$).

Discussion

A main finding of this study was that total fluid intake during the race was positively related to the changes in

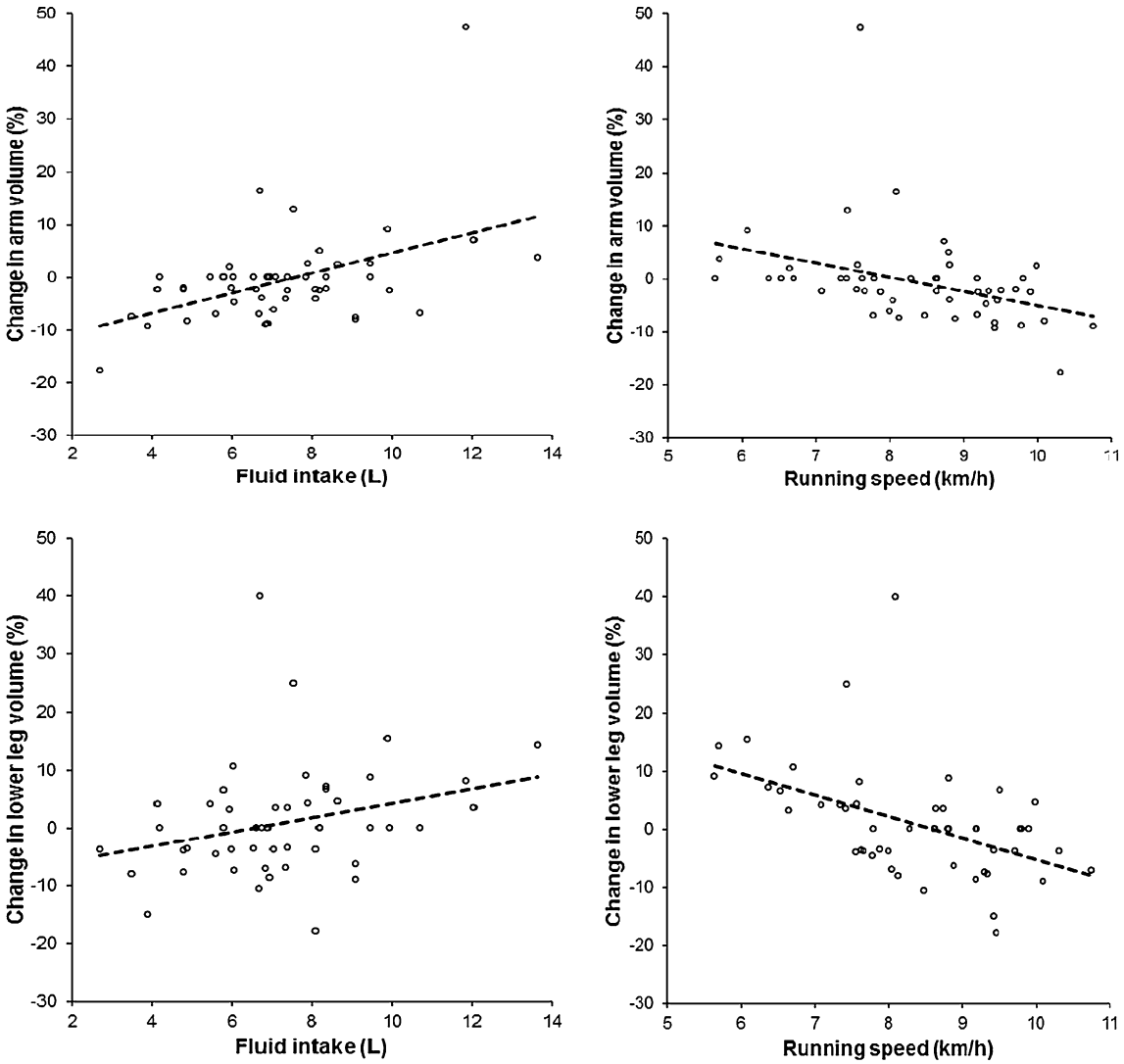

Fig. 2 Total fluid intake was significantly and positively associated with both the change in arm volume ($r = 0.46$, $p = 0.0007$) and the change in lower leg volume ($r = 0.29$, $p = 0.043$). Running speed correlated significantly and negatively to both the change in arm volume ($r = -0.37$, $p = 0.0091$) and the change in lower leg volume ($r = -0.47$, $p = 0.0005$) ($n = 50$)

both arm and lower leg volume where an increased fluid intake was associated with an increase in limb volumes. The changes in limb volumes were related to running speed where faster runners showed a decrease in limb volumes. Also, fluid intake was related to running speed where faster runners were drinking more. Obviously, faster runners were drinking more without the risk to develop peripheral oedemas. In addition, faster runners were drinking at a faster rate during the race as compared to slower runners and slower runners finished the race with lower levels of dehydration. Although faster runners were drinking more each hour, they were losing more body mass during the race presumably due to more sweating but they were still drinking appropriately at a relatively lesser rate than were the slower runners. While the changes in limb volumes were related to both total fluid intake and running speed but not to sodium intake, changes in fluid and electrolyte regulating hormones and renal function, the relative fluid overload in slower runners seems to be the most likely reason to develop peripheral oedemas.

Correlation of fluid and electrolyte intake with performance

The changes in volumes of both the arm and the lower leg correlated to total fluid intake during the race, but not to sodium intake (see Fig. 2). These athletes showed a variation of total fluid intake between 2.7 and 10.6 L during the race with a mean fluid intake of 7.3 L is equal to ~0.58 L/h. Running speed was significantly and negatively associated with the changes in both arm and lower leg volume (see Fig. 2). These findings allows us to support the

hypothesis of race duration as a risk factor for fluid overload, described by Chorley et al. (2007) for marathoners and by Noakes et al. (1988, 1990) for ultra-marathoners and possibly resulting in oedemas. The runners overdrink because they believe that if they do not they may die of 'dehydration' or that their performance will be impaired (Noakes 2011). Chorley et al. (2007) concluded that slower runners were more likely to overconsume fluids, augmented by their exposure to more environmental heat stress during the warmer part of the race. Recently, the same correlation between fluid intake and mean running speed was also shown by Knechtle et al. (2010a) in a 24 h ultra-marathon. In the present study, we found an increase in plasma volume which was associated with total fluid intake. As overhydration, or excessive fluid consumption, during activity is the major risk factor for EAH (Almond et al. 2005; Hew et al. 2003; Irving et al. 1991; Noakes et al. 1985; Noakes 2011), we assumed, therefore, that fluid intake was responsible for the development of oedemas.

Redistribution of the volume

The volume of both the lower leg and the arm showed no changes whereas the thickness of adipose subcutaneous tissue at *os metacarpale III*, *malleolus medialis*, and *os cuneiforme mediale* increased using the LIPOMETER®. We presume that the volume in the arm and lower leg showed no changes during the race because there was a redistribution of the limb volume limited to *dorsum mani* and *dorsum pedis* and not involving the whole limb. We found no relationship between the significant changes in the thickness of subcutaneous adipose tissue on *dorsum mani* and at *dorsum pedis* with the non-significant changes in the corresponding limb volumes. As the entire extremities were measured using plethysmography, we were not able to differentiate between arm and hand or between lower leg and foot, respectively.

Trauma to the feet from repetitive landing could reasonably result in injury and swelling of the feet. A further aspect is the centripetal force in the upper extremities while running and the gravitational force for the lower extremities. Another mechanism for developing oedemas, specifically the absence of oedemas in feet immediately after the race, but the development of them shortly afterwards which has also been described by Knechtle et al. (2009b), could be the fact that the athletes were wearing running shoes compressing their feet. Due to the compression, the development of oedemas of the feet during the race was prevented. When the shoes were removed, the fluid in the adipose subcutaneous tissue might be redistributed. After removing the shoes, the compression decreased and a redistribution of fluid from the lower leg into the foot, especially into the subcutaneous adipose tissue, could occur, leading to oedemas in the feet. Therefore, the volume of the lower leg showed no changes while the thickness of adipose subcutaneous tissue, measured at *malleolus medialis* and at *os cuneiforme mediale*, increased. The assumption of a redistribution of fluid into the subcutaneous adipose tissue of the hands and feet could be supported by the finding that we could not document any changes in thickness of subcutaneous adipose tissue at *arcus zygomaticus* in the face and at *margo medialis tibiae* at the lower leg above the foot.

Other potential pathophysiological mechanisms leading to peripheral oedemas

A slower race time seems to be associated with a change in both arm and lower leg volume. This might be due to the fact that these athletes were exposed for a longer time to running in an upright position, where the consequent gravitational force possibly led to more oedemas in both the hands and the feet. Apart from fluid overload, however, different other mechanisms could lead to a retention of total body water, and therefore, to an increase in limb volumes and a development of peripheral oedemas, such as protein catabolism with the development of hypoproteinemic oedemas (Lehmann et al. 1995), an increased protein synthesis leading to increased plasma volume (Maughan et al. 1985, Mischler et al. 2003), [Na^+] retention (Fellmann et al. 1999) due to an increased activity of aldosterone (Wade et al. 1981) or dehydration and impaired renal function due to skeletal muscle damage (Uberoi et al. 1991).

Milledge et al. (1982) described the activation of the renin-angiotensin-system and plasma aldosterone as a possible reason for the expansion in plasma volume and water retention possibly leading to oedemas. An increase in plasma volume due to sodium retention was mentioned by Fellmann et al. (1999). The change in serum [Na^+] in the present subjects showed a correlation with the change in serum copeptin concentration, a co-secreted cleavage product of vasopressin, but not with serum aldosterone concentration. In the presence of an increased blood osmolality, vasopressin is released (Hew-Butler 2010), explaining the increase in serum copeptin concentration during the race. Vasopressin reduces renal free water excretion by activating arginine vasopressin receptor 2 (AVPR2) in the collecting tubules and, as a result, urine osmolality also increases (Hew-Butler 2010; Verbalis 2007). Vasopressin should be suppressed in case of hyponatremia/hypervolemia (Hew-Butler et al. 2008). A fluid overload could be due to water retention caused by an inappropriate manner of vasopressin release (Hew-Butler 2010; Hew-Butler et al. 2008). In the present study, we found a positive relationship between serum copeptin

Table 3 Correlation matrix using Pearson correlation, p value is inserted in case of a significant correlation

	Change in thickness at *os metacarpale III*	Change in thickness at *malleolus medialis*	Change in arm volume	Change in lower leg volume
Fluid intake	0.11	−0.03	0.46, $p = 0.0007$	0.29, $p = 0.0430$
Sodium intake	0.22	−0.15	0.24	0.10
Change in plasma volume	−0.08	0.14	0.28, $p = 0.0497$	0.40, $p = 0.0041$
Change in aldosterone concentration	−0.04	−0.21	−0.20	−0.21
Change in copeptin concentration	−0.14	0.10	−0.19	−0.05

	Change in plasma [Na^+]	Change in fractional sodium excretion	Change in transtubular potassium gradient	Change in serum osmolality	Change in urine osmolality
Change in aldosterone concentration	0.08	−0.31, $p = 0.0283$	0.17	0.31, $p = 0.0276$	−0.05
Change in copeptin concentration	0.17	−0.19	0.12	0.28	0.16
Change in plasma volume	−0.19	0.35, $p = 0.0115$	−0.11	−0.32, $p = 0.0247$	0.11
Sodium intake	−0.05	0.10	−0.22	−0.14	−0.12
Fluid intake	−0.37, $p = 0.0086$	0.41, $p = 0.0030$	−0.23	−0.44, $p = 0.0015$	−0.14

concentration and urine osmolality, assuming that there was a physiological secretion of vasopressin. The changes in serum copeptin concentration were related to the changes in serum [Na^+]. In addition, post-race serum [Na^+] was neither related to post-race serum copeptin nor to post-race serum aldosterone concentration. We assume that post-race serum [Na^+] was not regulated due to hormones such as aldosterone and copeptin.

The intake of non-steroidal anti-inflammatory drugs (NSAIDs) is also a risk factor for EAH (Davis et al. 2001). NSAIDs use is common among athletes, being used by 50–60% (Hew et al. 2003). These drugs are known to increase the potential effects of vasopressin by inhibiting renal prostaglandin synthesis via the Cyclooxygenase-2 (COX-2) isoform of cyclo-oxygenase (Breyer et al. 1990; Hebert et al. 1990). NSAIDs decrease the glomerular filtration rate when given to those with effective volume depletion, such as exercising endurance athletes (Patrono and Dunn 1987). The urine-diluting capacity of the kidney may be impaired by these effects. These theoretical considerations, such as NSAIDs as a risk factor for EAH, remain controversial as, for example, Almond et al. (2005) found no association between the uses of NSAIDs with the development of EAH in runners in the 2002 'Boston Marathon'. In contrast to Almond et al. (2005); Wharam et al. (2006) demonstrated a significant association. Therefore, the role of NSAIDs in the development of EAH remains controversial but in some runners it is a potential risk factor for EAH. Unfortunately, these athletes were not asked about their consumption of NSAIDs.

There are medical risk factors in the general population that may also play a role in developing EAH and therefore leading to water retention. Rosner (2004) described an altered renal water excretory capacity potentially impaired by drugs such as serotonin-specific reuptake inhibitors (SSRIs) and diuretics as a risk factor for EAH. Medications such as selective serotonin re-uptake inhibitors or thiazide diuretics, associated with hyponatremia in non-athletes, but not known to increase the development of EAH, may be possibly important clues to the pathogenesis of EAH (Rosner and Kirven 2007). Altered renal function caused by intrinsic renal disease, a risk factor for the development of hyponatremia in the general population that may also play a role in EAH was described by Ayus et al. (1982). Hyponatremia could lead to overhydration due to a vasopressin release. Schwartz et al. (1957) described the syndrome of inappropriate antidiuretic hormone hypersecretion (SIAHD) as another risk factor. In SIADH, the release of vasopressin is not inhibited by a reduction in plasma osmolality. Therefore, overdrinking causes hyponatremia if there is also SIADH present (Noakes et al. 2005).

In the present study, urine excretion significantly increased during the race as compared to pre-race, and

became reduced post-race, reaching pre-race levels only on day 3 after the race. During the race, the athletes voided ~120 ml of urine per hour. When the athletes voided more than 500 ml in 24 h then their fluid intake during the race was excessive by that additional amount since obligatory urinary losses are about 500 ml per 24 h. The kidney needed about 3 days post-race to recover and to function as before. This fact has already been described by Knechtle et al. (2009a). For urine, the increase in osmolality, matching the fact that athletes urinated less frequently, was significantly related to the increase in urea and to the decrease in sodium. An overhydration could possibly lead to oedemas in the extremities. Therefore, we assume that an altered renal function could also be a part of the mechanism leading to peripheral oedemas.

Prevalence of exercise-associated hyponatremia

A further finding was that no athlete suffered EAH. Except for two successful finishers, all athletes finished with an increased serum [Na^+]. The remaining two athletes showed an over-hydration already at the start with a serum [Na^+] pre- as well as post-race <135 mmol/L. Regarding the association between the change in body mass and post-race serum [Na^+], we found a significant and negative correlation (see Fig. 1). Serum [Na^+] increased by 1.6% and body mass decreased by 1.9 kg. This negative correlation between the change in body mass and post-race serum [Na^+] corresponds to results in former studies, where athletes with less weight loss (or weight gain) showed lower serum [Na^+] (Mettler et al. 2008; Noakes et al. 2005; Sharwood et al. 2004; Speedy et al. 1997a, b, 1999).

Furthermore, we found a significant and negative correlation between post-race serum [Na^+] and fluid intake (see Fig. 1); athletes who drank less during the race showed higher post-race serum [Na^+]. These findings support the existing data in the studies of Noakes et al. (1985, 2011); Irving et al. (1991) as well as the different studies of Speedy et al. (1997a, 1999, 2000a, b, c, 2001) in the pathogenesis of EAH. Fluid overload, as a consequence of excessive drinking, was described several times as the main risk factor in the pathogenesis of EAH (Almond et al. 2005; Hew et al. 2003; Noakes et al. 1985). Therefore, athletes are recommended by the 'Position Statement' of the 'International Marathon Medical Directors Association' (Noakes 2003) to drink ad libitum between 0.4 and 0.8 L/h during a race, which was followed by our athletes consuming ~0.58 L/h on average despite the high frequency of refreshment stations during this race.

Additionally, this study supports the important findings in the reports of Hew-Butler et al. (2006); Speedy et al. (2002) and Noakes (2011) describing no correlation between sodium intake, post-race serum [Na^+] and the change in serum [Na^+]. While Hew-Butler et al. (2006) investigated the change in serum [Na^+] with sodium or placebo supplementation as compared to a group without supplementation and normal eating and drinking habits, Speedy et al. (2002) investigated a group using only salt supplementation. Hew-Butler et al. (2006) reported no significant differences in serum [Na^+] in their different groups and Speedy et al. (2002) described no correlations with salt supply and the change in serum [Na^+]. Almond et al. (2005) also showed that sodium ingestion was not protective against EAH in runners in the 2002 'Boston Marathon'. Finally, Noakes (2011) stated clearly that EAH during an endurance exercise cannot be prevented by ingestion of a sodium-containing sports drink.

Are the applied methods reliable?

Lastly, we could also explain the findings of the disparate results in limb volumes and thickness of subcutaneous adipose tissue of the extremities as a potential limitation of the applied method of plethysmography while measuring the volumes of both the lower leg and arm. The method of measuring limb volume using plethysmography is similar to the method chosen by Lund-Johansen et al. (2003) measuring the displaced water by weighing. Lund-Johansen et al. (2003) concluded that water displacement volumetry was a sensitive method for the measurement of leg volume. Therefore, we assumed that measuring changes in limb volumes using plethysmography was an accurate method for the quantification of oedemas of the whole limb. The thickness of subcutaneous adipose tissue was measured using a LIPOMETER® as described by Jürimäe et al. (2007). The LIPOMETER® is a non-invasive examination using infrared. Different investigators have already used the LIPOMETER® in their studies. Tafeit et al. (2009) described the LIPOMETER® as a non-invasive, quick, precise and safe measurement of subcutaneous adipose tissue at any site in the human body. Furthermore, Möller et al. (2000) used the LIPOMETER® in their study, and documented that the technique allowed a precise determination of the distribution of subcutaneous adipose tissue at specified body sites. Therefore, we assume the LIPOMETER® as an accurate method for the identification of the thickness of subcutaneous adipose tissue.

Limitations and implications for future research directions

A limitation of this study might be the limited method of measuring the extremities volume by using a plethysmography, as mentioned above. By using the plethysmography for the whole limb, we were not able to distinguish between arm and hand or the lower leg and foot results,

respectively. Technically, this approach would not measure precisely the same limb length if there had been a change in volume. A more appropriate approach for that would be to measure the volume loss from a full container after the limb has been inserted. In future studies, the volume in hands and feet instead of arms and lower legs should be measured using plethysmography to confirm our assumptions. Slight changes in the water distribution of the body influencing the thickness of the dermis under various physiological conditions have also been shown by Eisenbeiss et al. (2001) by measuring thickness and echodensity using high-frequency ultrasound. In future studies, the effect of compression stockings on the development of peripheral oedemas in ultra-marathoners might be investigated (Kemmler et al. 2009). A further limitation may be the fact that food and drink diaries were only recorded by the runners. Experts experience has shown that an accurate collection of such data can be very difficult (Rehrer et al. 2010). We measured a part of the fluid loss such as urine excretion, but do not know sweat rate and would need to estimate endogenous fluid production to complete a fluid balance.

Conclusions

To summarise, a relationship between fluid intake and changes in both arm and lower leg volumes was found. An increase in both the lower leg and arm volume could be demonstrated in athletes with an increased fluid intake. We found no athlete developing EAH. Therefore, we concluded that our athletes did not generally believe they need to drink as much as possible during an exercise, rather they were drinking only in response to their thirst. Since we found no association between endocrine and renal parameters with the changes in limb volumes, fluid overload is the likely mechanism leading to an increase in limb volumes. For practical application, when an athlete drinks more than he needs, that fluid will eventually end up in his limbs. Due to the disparate findings of changes in limb volumes using plethysmography and thickness of subcutaneous adipose tissue, the measurements of changes in limb volumes should be restricted in future studies to hands and feet.

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