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Effect of sodium administration on fluid balance and sodium balance in health and the perioperative setting. Extended summary with additional insights from the MIHMoSA and TOPMAST studies

Niels Van Regenmortel, MD, PhD [a,b,*], Thomas Langer, MD [c,d], Tim De Weerdt, MD [e], Ella Roelant, PhD [f,g], Manu Malbrain, MD, PhD [h], Tim Van den Wyngaert, MD PhD [i,j], Philippe Jorens, MD, PhD [a,j]

[a] Department of Intensive Care Medicine, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Antwerp, Belgium
[b] Department of Intensive Care Medicine, Ziekenhuis Netwerk Antwerpen Campus Stuivenberg, Lange Beeldekensstraat 267, B-2060 Antwerp, Belgium
[c] Department of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy
[d] Department of anesthesia and Intensive Care Medicine, Niguarda Ca' Granda, Milan, Italy
[e] Department of Nephrology, Kliniek Sint-Jan, Kruidtuinlaan 32, B-1000 Brussels, Belgium
[f] StatUa, Center for Statistics, University of Antwerp, Prinsstraat 13, B-2000 Antwerp, Belgium
[g] Clinical Trial Center (CTC), CRC Antwerp, Antwerp University Hospital, University of Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium
[h] First Department of anesthesia and Intensive Therapy, Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
[i] Department of Nuclear Medicine, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Antwerp, Belgium
[j] Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Antwerp, Belgium

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ABSTRACT

Purpose: We aimed to provide an extended analysis of the physiological handling of of the sodium burden induced by maintenance fluids.
Materials and methods: We revisited two studies that demonstrated, in healthy volunteers and in surgical patients, that maintenance fluids with 154 mmol/L of sodium lead to a more positive fluid balance than a regimen containing 54 mmol/L. We report different unpublished data on the renal handling of the imposed sodium burdens with specific attention to the resulting fluid and sodium balances.
Results: The kidneys adapt to the sodium-rich fluids not only by altering sodium excretion, but also by retaining extra free water by concentrating urine. Realigning urinary sodium excretion with an increased administration takes around one day in health and much longer in the clinical setting. This difference may be explained by the presence of hypovolemia-induced aldosterone secretion in the latter group. Non-osmotic storage of sodium limits an unrestrained fluid retention even when very high amounts of sodium are administered but fluid accumulation will inevitably be further prolonged.
Conclusions: Sodium administration induced by sodium-rich maintenance fluids leads, especially in the clinical setting, to prolonged fluid retention when compared with a regimen that resembles a healthy dietary sodium intake, even when kidney function is normal.

1. Introduction

Intravenous maintenance fluids are prescribed to cover the daily needs of water, glucose and electrolytes when hospitalized patients are temporarily unable to ingest food or fluids [1]. Several studies have demonstrated that maintenance fluids are among the largest sources of water, sodium and chloride in both the adult and pediatric critical care environment [2-4]. Therefore, and in view of the well-described clinical problem of fluid accumulation (iatrogenic or otherwise), maintenance fluid therapy deserves a critical reappraisal [5,6]. In particular, the sodium content of maintenance solutions is the subject of vivid debate [7]. Some advocate the use of hypotonic fluids since an isotonic maintenance fluid strategy contains much more sodium than humans usually ingest through a healthy diet [8]. Opponents of a hypotonic maintenance fluid strategy point out the dangers of hyponatremia [9].

Recently, we published two studies that focused on the sodium content of maintenance fluid therapy: the MIHMoSA crossover experiment

* Corresponding author at: Lange Beeldekensstraat 267, B-2060 Antwerp, Belgium.
E-mail address: niels.vanregenmortel@uza.be (N. Van Regenmortel).

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Table 1
Detailed composition of the study fluids.

	Na154	Na54
Sodium (mmol/L)	154	54
Chloride (mmol/L)	194	55
Potassium (mmol/L)	40	26
Phosphate (mmol/L)	–	6.2
Magnesium (mmol/L)	–	2.6
Lactate (mmol/L)	–	25
Osmolarity (mOsm/L)	614	430
Tonicity (mmol/L)	373[a]	162[b]
Strong Ion Difference (mEq/L)	0	± 30[c]
Glucose (g/L)	50	50

Na154 is NaCl 0.9% in glucose 5% supplemented by 40 mmol/40 mL KCl per liter, Na54 is Glucion 5%® (Baxter, Deerfield, Illinois, USA).

[a] 154 + 194 + 40 mmol/1.040 L (including additional volume of KCl).

[b] 54 + 55 + 26 + 6,2 + 2,6 + 25 mmol/1.040 L (40 mL of aqua was added per liter of fluid for blinding reasons).

[c] Assuming complete lactate-metabolism after intravenous administration.

(Metabolism of Isotonic versus Hypotonic Maintenance Solutions in Adults) in healthy volunteers and the randomized controlled TOPMAST trial (Tonicity of Perioperative Maintenance SoluTions) in patients undergoing major thoracic surgery before being admitted to the intensive care unit (ICU) [10,11]. In each of the studies, two different maintenance fluid strategies were compared regarding their impact on cumulative fluid balance. Both studies demonstrated an increased fluid retention under sodium-rich maintenance fluid therapy. The aim of the present report is therefore to provide additional insights regarding the role of the sodium content of maintenance fluids on sodium and water handling, both in healthy volunteers and surgical patients admitted to the ICU.

2. The difference in fluid balance caused by the sodium content of the fluid regimen is comparable in health and in the clinical setting

During the MIHMoSA crossover experiment, cumulative fluid balance was measured in 12 healthy volunteers who refrained from any oral intake during two separate study periods of 48 h [10]. They were administered glucose-containing maintenance fluids with 154 mmol/L (Na154) or 54 mmol/L (Na54) of sodium at a guideline-recommended rate (25 mL/kg/day) (detailed composition: see Table 1). Using a comparable study design and the same fluids at a rate of 27 mL/kg/day, cumulative fluid balance was assessed in 70 patients admitted to the ICU after having undergone major thoracic surgery during the double-blind, randomized controlled TOPMAST trial [11]. The study treatment started before surgery and ended when the patients were discharged from the ICU (at 8 AM of the third postoperative day at the latest) or when an adverse event occurred (e.g. the need for diuretics). The mean treatment duration was 39 h (SD 16.0). During the TOPMAST study, the prescription of resuscitation fluids was at the discretion of the treating physicians, but their volume and sodium content were recorded. Table 2 shows a direct comparison between the subjects of both studies and includes all relevant data on fluid and sodium intake and output of both studies. It is important to acknowledge that all participants in both studies had a normal kidney function: an estimated glomerular filtration rate (eGFR) low than 60 mL/min/m^2 (CKD-EPI) was an exclusion criterion and the mean eGFR was 104 mL/min/m^2 in the Na54 arm and 107 mL/min/m^2 in the Na154 arm.

The main findings of both studies were strikingly comparable despite the different setting: net cumulative fluid balance was significantly more positive under sodium-rich compared to sodium-poor

Table 2
Patient and treatment characteristics of the MIHMoSA and TOPMAST trials.

	MIHMoSA		TOPMAST	
	Na54	Na154	Na54	Na154
Baseline characteristics				
Participants (n)	12 (crossover design)		34	35
Age (years)	35 (10)		63 (9)	62 (7)
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)	110 (13)		104 (21)	107 (26)
Mean duration of treatment period (hours)	48		39 (16)	39 (17)
Fluid administration				
Study fluid rate (mL/kg/d)	25		27	
Study fluid volume	3476 (823)	3474 (822)	3266 (1410)	3242 (1489)
Off-study fluid gain[a]	0	0	1683 (1022)	1743 (1098)
Total fluid gain (mL)	3476 (823)	3474 (822)	4948 (1851)	4986 (2226)
↪Between-treatment difference (mL)	−2 (95%CI-10-6)		37 (95%CI −948-1022)	
Total fluid gain per hour (mL/h)	72 (17)	72 (17)	129 (30)	132 (27)
Fluid balance				
Estimated cumulative fluid balance at 48 h (mL)	162 (95%CI −34-357)	751 (95%CI 555-947)	2349 (95%CI 1994–2705)	3236 (95%CI 2877–3595)
↪Between-treatment difference (mL)	590 (95%CI 450–729)		887 (95%CI 380–1394)	
Difference in body weight at end of study (g)	−1689 (780)	−1103 (1144)	N/A	N/A
↪Between-treatment difference (g)	586 (95%CI 198–973)		N/A	
Sodium administration				
Study fluid sodium (mmol)	188 (44)	535 (127)	180 (78)	499 (229)
Off-study sodium gain (resuscitation fluids minus drain outputs)	0	0	159 (126)	123 (107)
Total sodium gain (mmol) (all fluids minus drain outputs)	188 (44)	535 (127)	339 (134)	622 (246)
↪Between-treatment difference (mmol)	347 (95%CI 301–394)		283 (95%CI 188–379)	
Total sodium gain per hour (mmol/h)	4 (1)	11 (3)	9 (4)	17 (4)
Sodium balance				
Urine sodium (mmol)	311 (104)	503 (216)	161 (101)	210 (145)
Estimated cumulative sodium balance at 48 h (mmol)	−132 (95%CI −179-84)	39 (95%CI −8-87)	225 (95%CI 169–282)	546 (95%CI 489–602)
↪Between-treatment difference (mmol)	171 (95%CI 155–188)		320 (95%CI 240–400)	

Mean values are reported with their standard deviations between parentheses. None of the reported baseline characteristics or fluid administration characteristics were significantly different between the two study treatments at a 5% significance level. 95%CI = 95% confidence interval. Adapted from Van Regenmortel et al. and Van Regenmortel et al., with permission. [10,11].

[a] Off-study fluid balance is calculated as the end-of-study difference between all non-study fluid intake (resuscitation fluids during and after surgery and oral intake) and output (blood loss and drain outputs)

maintenance fluids. Fig. 1 shows the primary endpoint of the two studies as reported in the original papers, rescaled for an optimized comparison. In MIHMoSA, cumulative fluid balance after 48 h was 590 mL (95% CI 450–729) more positive under Na154 compared to Na54. In TOPMAST, the estimated cumulative fluid balance at 48 h was 887 mL (95% CI 380–1394) more positive in the Na154 arm, despite comparable non-study fluid sources and fluid losses through drain outputs in both study arms.

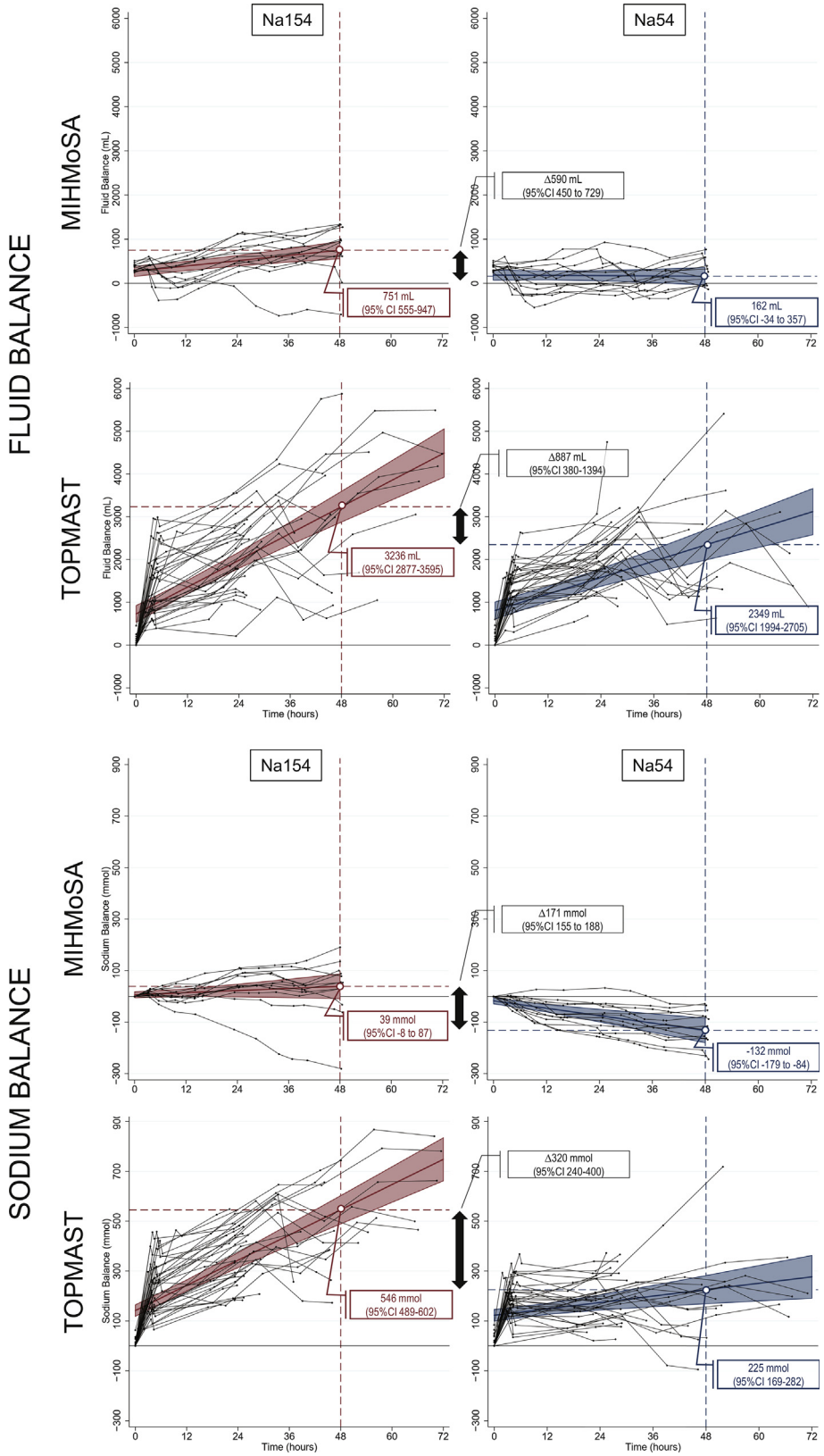

Fig. 1. Estimated cumulative fluid and sodium balances of the MIHMoSA and TOPMAST trials. Adapted with permission from Van Regenmortel et al. and Van Regenmortel et al. [10,11].

3. How do kidneys handle an additional sodium burden in health?

3.1. Kidneys excrete sodium inefficiently when the administered amounts are far from one's usual dietary intake

The renal capability to adapt to altered sodium intakes depends on an individual's usual dietary sodium ingestion. When the normal amount is changed abruptly and substantially, it takes several days to realign sodium excretion with intake [12]. This well-described delay was demonstrated already many years ago and leads to a body weight gain due to fluid retention when sodium balance is positive, and body weight loss when sodium intake is decreased [13]. Normal dietary sodium intake depends on personal and cultural preferences. There are large variations in sodium intake throughout the world, with medians from 1 to 246 mmol per day [14]. As a comparison, a typical amount of 2 L of isotonic maintenance fluids (e.g. NaCl 0.9% or Ringer's lactate) contains 260–308 mmol of sodium (which corresponds to 6-7 g), and will thus almost always lead to sodium-induced fluid retention [8].

The usual dietary sodium intake of the MIHMoSA participants was estimated from a dedicated 24-h urine collection and was found to be around 124 mmol per day (IQR 86–176 mmol). The sodium-rich maintenance fluid therapy was responsible for a sodium burden of 267 mmol (SD 63) per day, substantially higher than the usual dietary habits of the studied subjects. The sodium-poor regimen provided 94 (SD 22) mmol per day. Fig. 2 illustrates the gradual increase in urinary sodium excretion, seemingly reaching a plateau at around 200 mmol/L after approximately 24 h. The delay in realigning sodium excretion with intake when receiving Na154 is in sharp contrast with the almost instantaneous adaptation of potassium excretion to the administered dose (Fig. 2). Under Na54, the urinary sodium excretion decreases slightly but overall does not change much from baseline, demonstrating that the amount of sodium provided by this solution is somewhat lower but not far from the subjects' usual daily intake. The resulting fluid and sodium balances are illustrated in Fig. 1 and show a 750 mL fluid gain in the Na154 arm and an almost zero fluid balance under Na54. In the Na54 arm, sodium balance was negative, which is explained by the lower-than-dietary sodium intake. Interestingly, during the study, where subjects refrained from any oral intake for 48 h, a loss of body weight was found under both treatments (Table 2). Probably, the undernutrition during the study contributed to this weight loss. We presume there must have been an equal non-water body weight loss due to the 48 h of fasting (and continuing insensible and fecal losses)

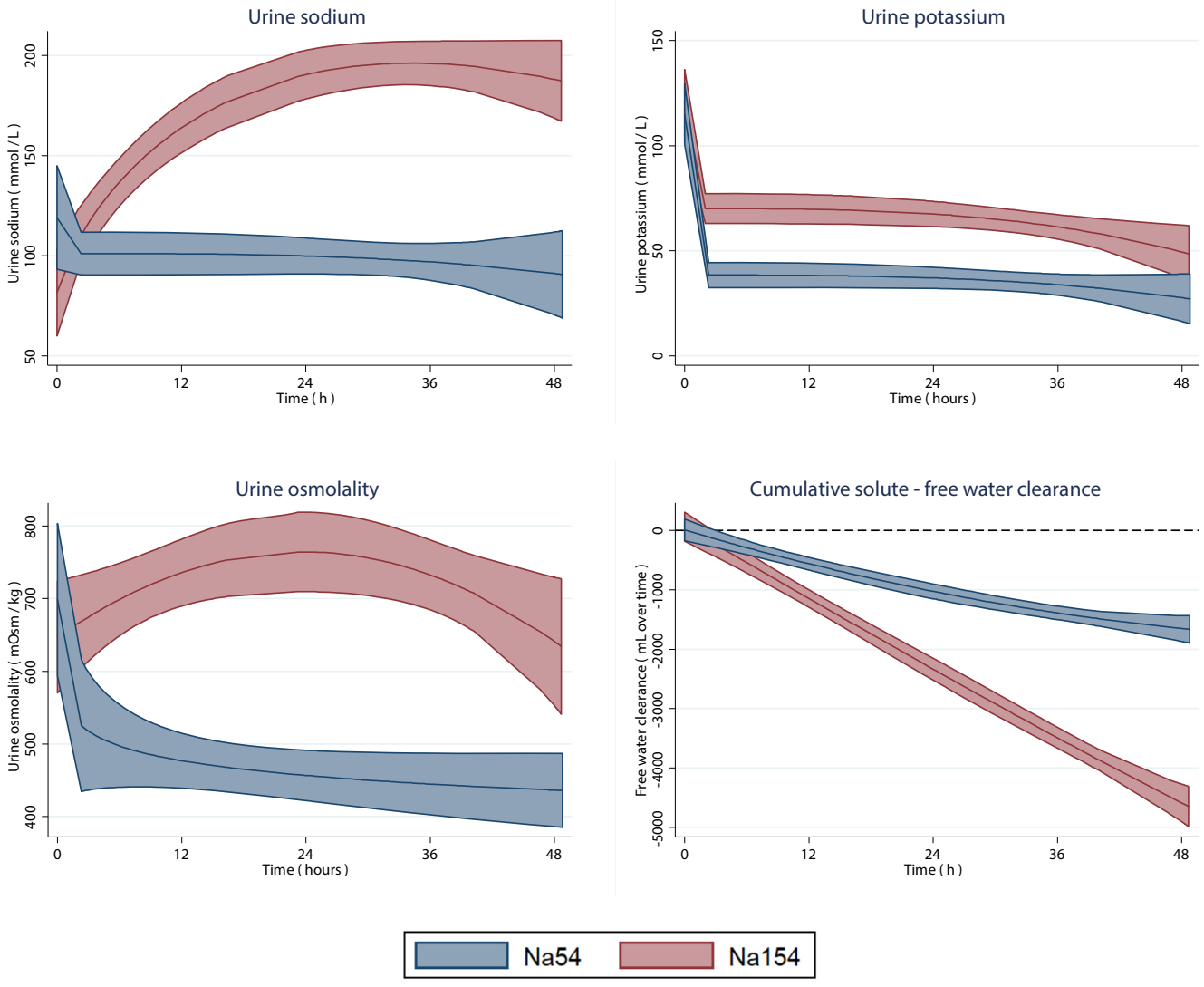

Fig. 2. Sample-by-sample measurement of urinary sodium, potassium and osmolality, and the calculated cumulative solute-free water clearance (FWC) encountered during the MIHMoSA study. Solute-free water clearance is expressed as the cumulative volume of free water that is retained (negative value) or excreted (positive value) over the course of the complete study period. For representational purposes, the raw data are shown as fractional polynomial prediction plots; shaded areas resemble 95% confidence intervals.

under both treatments superimposed on a net water loss in the Na54 arm and a net water gain in the Na154 arm.

The physiological role of sodium in water homeostasis has been centered throughout evolution around the protection against dehydration, and as a consequence, even healthy kidneys cannot increase urinary sodium concentration above 250–300 mmol/L [13]. If salt intake is increased above this threshold, the kidneys reach their maximum level of sodium concentration and the new steady-state may require an increased urinary volume and thus additional water intake [13]. Although the administration of even isotonic fluids (140–154 mmol/L of sodium) provide the necessary water to remain under this concentration threshold, the co-administration of hypertonic solutions (e.g., in traumatic brain injury) or sodium-rich medications (e.g., many antibiotics and effervescent oral medications) could lead to the impossibility to excrete sodium and thereby induce excessive sodium-induced fluid retention.

3.2. Where does the water that contributes to the positive fluid balance come from?

The participants of the MIHMoSA study were not allowed to eat or drink during the experiment. It was thus impossible that the retained fluid in the Na154 arm was delivered by an increased ingestion of water. The fluid retention must thus have been induced by an increased renal water reabsorption. This is illustrated by the subjects' urinary osmolalities (Fig. 2). In the Na154 arm, urine osmolality reached a plateau after 12–24 h, reaching values of ±750 mOsm/kg. In the Na54 arm, urine osmolality dropped to ±450 mOsm/kg. This difference in urinary osmolality (around 300 mOsm/kg) is larger than would be expected by the osmolality exerted by the administered electrolytes (the tonicity of Na154 is 373 mOsm/kg; of Na54 it is 169 mOsm/kg, a difference of around 200 mOsm/kg, see Table 1). This indicates an additional concentration of urine and thus an increased reabsorption of free water. We substantiated this by calculating solute-free water clearance (FWC), a measure of the quantitative ability of the kidneys to excrete or retain water over a certain period of time (Fig. 2) using the following formula $C_{H2O} = \textit{urine volume over the time since the last sample} \times \left(1 - \frac{Uosm}{Posm}\right)$, where U_{osm} is the urine osmolality and P_{osm} is the plasma osmolality. A urine osmolality that is higher than plasma indicates the concentration of urine and the reabsorption of free water. To end up with the cumulative FWC, we added the values of subsequent samples sequentially to the first one, so that the FWC-graph in Fig. 2 illustrates the total amount of absorbed or excreted free water (negative and positive values, respectively) over the whole study period. While even under Na54 the kidneys concentrate urine to retain free water, water reabsorption is substantially larger under Na154. The question whether pushing the kidneys to the limits of their ability to concentrate urine imposes separate health risks is still open for debate. Researchers studying the optimal amount of water ingestion have suggested to keep urine osmolality below the threshold of 500 mOsm/kg [15,16]. Studies performed in animals and in healthy adults have convincingly demonstrated that the concentration of urine, necessary to excrete large sodium burdens is an energy-consuming, glucocorticoid-centered, catabolic process [17,18]. Fact remains that neither NaCl 0.9% nor the isotonic balanced solutions (e.g. Ringer's lactate) provide any free water, although it is one of the main purposes of maintenance fluid therapy [19].

4. Why is there a large difference in fluid balance between the MIHMoSA and the TOPMAST studies?

4.1. Major surgery or severe illness leads to a positive fluid balance by nature

Not unexpectedly, the absolute cumulative fluid balances at 48 h in both treatment arms were much higher in TOPMAST's clinical setting (2349 mL under Na54 and 3236 mL under Na154 after 48 h) compared to MIHMoSA's healthy volunteers (162 mL under Na54 and to 751 mL under Na154 after 48 h) (Table 2 and Fig. 1). Reasonably, the vast difference in the cumulative administered volumes and sodium burdens might have played a substantial role. In MIHMoSA, there were no other fluid sources, whereas the patients in the TOPMAST study had a median off-study fluid gain (resuscitation fluids and oral intake minus blood loss and drain outputs) of around 1.5 L in both groups. Yet, even when taking the volume of these non-study fluid volumes into account, mean fluid balances were still much higher in the TOPMAST trial than in the MIHMoSA experiment. Two different explanations are possible: [1] the patients in TOPMAST received too many fluids, which the patients were not able to excrete or [2] the administered volumes were retained by the kidneys *on purpose* and were possibly even insufficient to deal with the vasodilation/hypovolemia associated both with the surgical and anesthesiologic procedures and with the surgical stress-induced alteration of endothelial permeability [20]. We are convinced the latter explanation is the most plausible. Indeed, the presence of an impaired endothelial glycocalyx was suggested by the marked decline in serum albumin levels. Of note, this reduction was not observed in the healthy volunteers of the MIHMoSA study (Fig. 3). Furthermore, our perioperative fluid regimen was already within the restrictive range, as suggested by the aldosterone peak (Fig. 3) at the end of surgery in both treatment arms, indicating an avid renal sodium and fluid retention. This hypovolemia could be due to blood loss, capillary leakage or the vasodilatation induced by general or epidural anesthesia. In contrast, in the MIHMoSA study, aldosterone levels decreased from baseline under Na154, pointing at an expansion of the intravascular compartment or at least an enhanced kidney perfusion.

These findings illustrate that fluid balance needs to be interpreted with caution in clinical practice. Even a markedly positive fluid balance does not necessarily indicate a detrimental or iatrogenic fluid accumulation and is often unavoidable or even a therapeutic target in different disease states and perioperative settings. It involves a combination of physiological processes that aim to cope with certain clinical realities such as hypovolemia, vasodilation, and capillary leakage. This view of fluid balance as a biomarker of severity of disease is perfectly compatible with the well-known association between a positive fluid balance and morbidity [21]. A one-sided view of fluid balance as a iatrogenic problem or a simple target for fluid therapy (or the use of diuretics for that matter) imposes different problems. We believe this is illustrated by the RELIEF trial, where patients in the restrictive fluid arm were more prone to develop AKI [22]. An adjunct substudy of the ARDSNet Fluid and Catheter Treatment trial (FACTT) showed that enrollment in the conservative fluid management arm, including a liberal treatment with diuretics, was associated with the development of long-term cognitive impairment and executive dysfunction [23]. Both studies demonstrate the dangers of ill-considered, all-too-restrictive fluid strategies.

4.2. How is this reflected in sodium excretion and sodium balance?

Fig. 4 clearly illustrates the striking difference between the urinary excretion of sodium in health compared to the perioperative setting. During the MIHMoSA experiment, urinary sodium excretion in the Na154 arm gradually increased to a concentration where a normal urine volume is sufficient to excrete the extra sodium burden. Sample-by-sample measurements of sodium balance show that sodium output matches intake again near the end of the 48 h study period. Cumulative sodium balance remains positive under Na154 and negative under Na54, explaining the difference in fluid balance and in body weight. In contrast, urinary sodium excretion and sodium balance during the TOPMAST study show a completely different picture (Fig. 4), even though MIHMoSA's Na154 arm ended up being administered even more sodium than TOPMAST's Na54 arm. In the first 12–24 h of the TOPMAST study, a drop in sodium excretion was observed in both treatment arms, presumably due to an increased (hypovolemia/

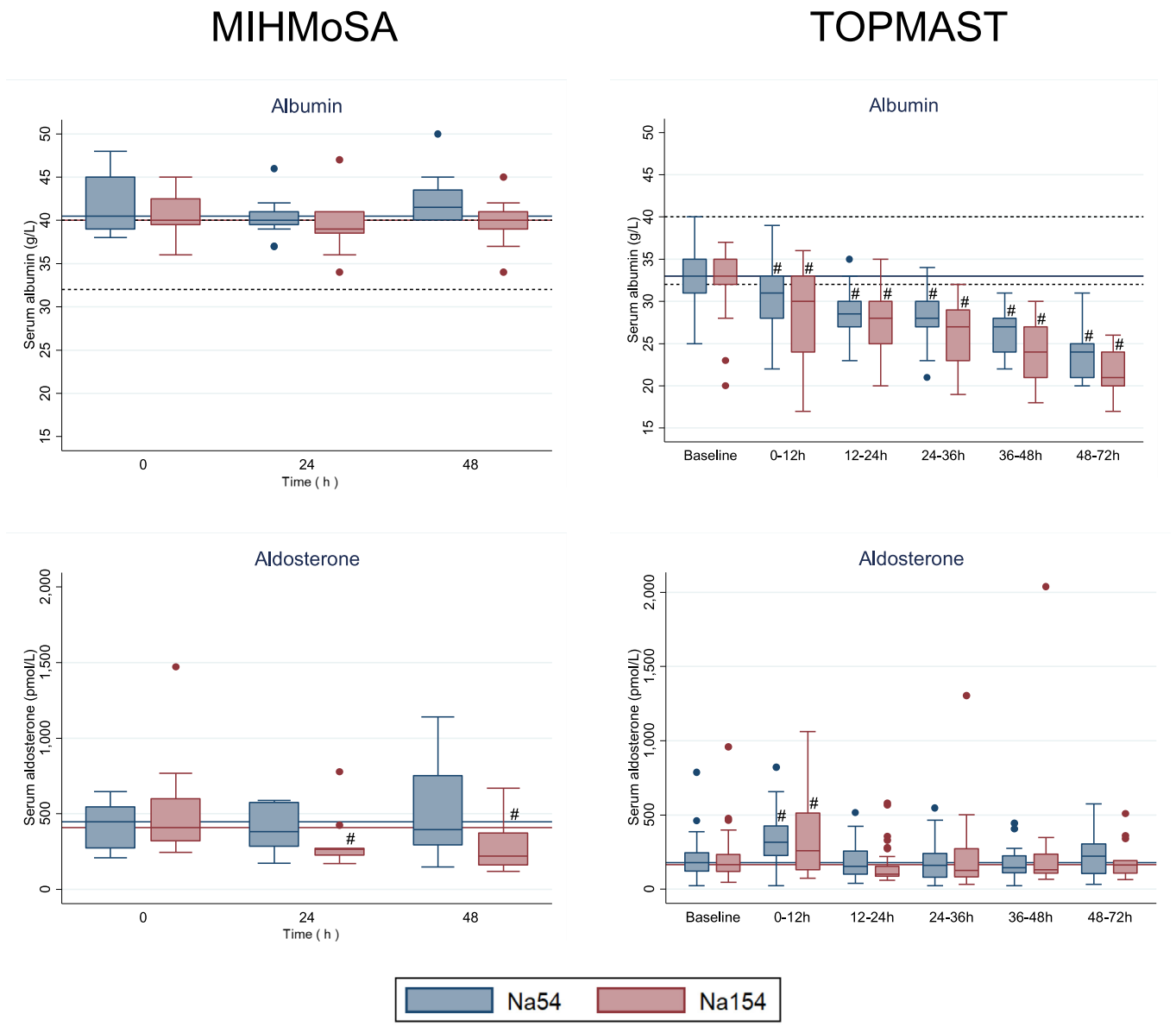

Fig. 3. Albumin and aldosterone concentrations over the course of the MIHMoSA and TOPMAST studies. # = significantly different from T_0 on a fluid-specific level ($p < 0.05$). Coloured lines resemble median value at T_0 for each fluid.

vasodilatation-induced) aldosterone secretion at that moment (Fig. 3). During the second half of the first day, urinary sodium excretion started to increase again, but never reached the concentrations necessary to excrete the additional sodium burdens. Even after 72 h in the Na154 arm, after substantial amounts of sodium had been administered, urinary sodium concentration was lower than 150 mmol/L. Although at this time the sample-per-sample sodium balance in the Na154 arm demonstrated a realignment of output with intake, but – in the presence of sustained treatment with Na154, cumulative sodium balance kept rising in view of the ongoing study treatment, not even reaching a plateau after 72 of treatment. Since the patients were followed for a maximum of 72 h during the study, it is unclear from the current data at what point the kidneys would have regained control of cumulative sodium balance. This is in contrast with the subjects in the Na54 arm, who were able to match excretion with intake after around 24 h and to keep sodium balance around 150 mmol above the zero-sodium balance baseline. Of note, surgical patients frequently receive less sodium during a shorter time than some critically ill patients that are admitted to the ICU. This makes sodium-rich maintenance fluids even more undesirable in the latter clinical setting, especially when they are unable to assist sodium excretion by oral water intake [8,24].

5. Why did the extremely positive sodium balances under Na154 in TOPMAST not lead to a larger difference in fluid balance?

The TOPMAST trial illustrates how easy it is to reach high sodium burdens resulting in very positive sodium balances, even during short-term admissions. Indeed, even when considering the sodium losses through blood loss or via surgical drains, 339 mmol (SD 134) of sodium was administered in the Na54 arm and 622 mmol (SD 246) in the Na154 arm (Table 2). It seems idiosyncratic that the vast between-treatment difference in sodium balance of the two studies (MIHMoSA 171 mmol; TOPMAST 321 mmol after 48 h) did not lead to a comparable difference in fluid balance (MIHMoSA 590 mL; TOPMAST 887 mL) (Table 2, black arrows in Fig. 1). This finding suggests that sodium-induced fluid retention is eventually limited, even in the presence of persisting sodium administration.

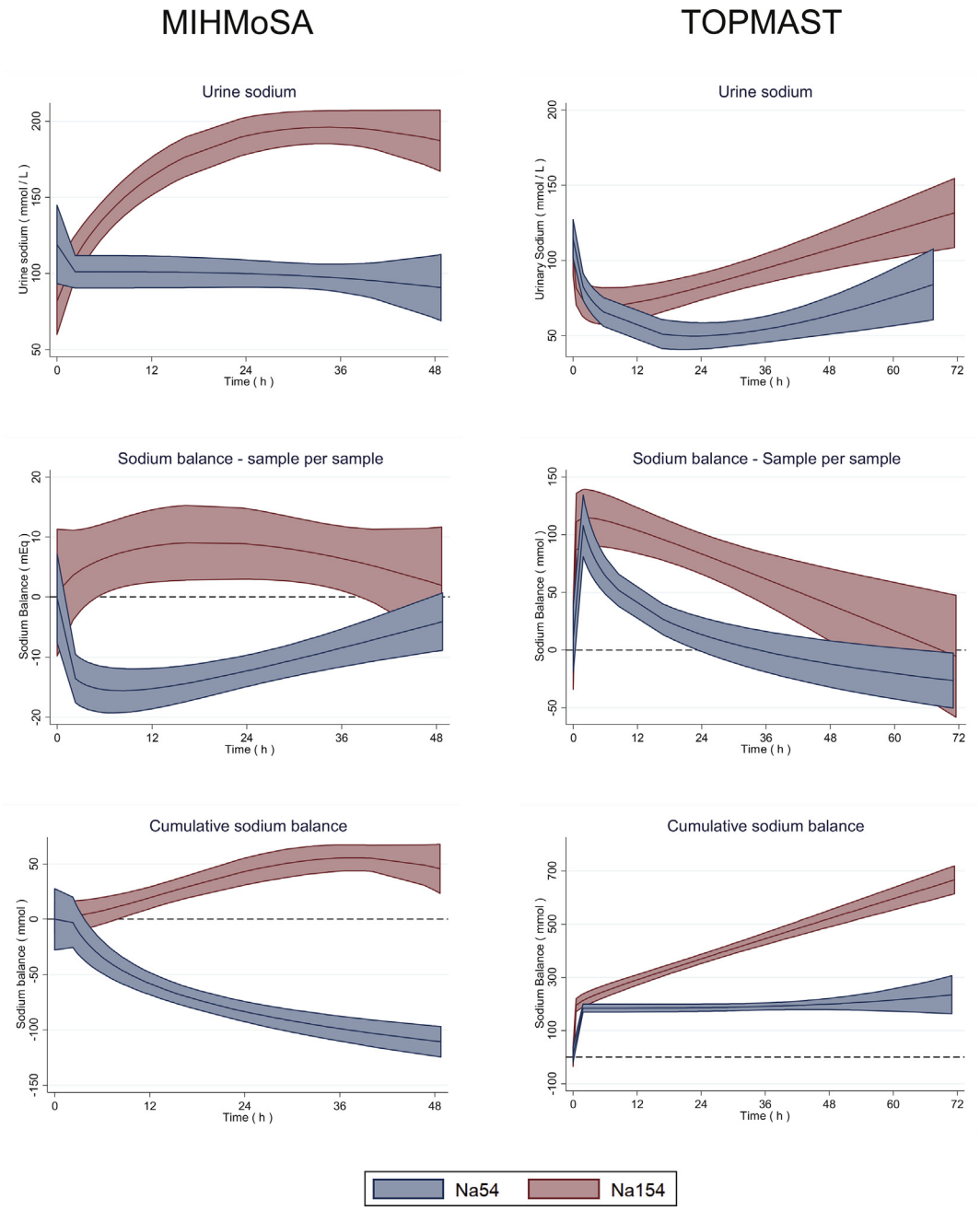

Fig. 4. Sample-by-sample urinary sodium and sodium balance, and the cumulative sodium balance encountered during the MIHMoSA and TOPMAST studies. For representational purposes, the raw data are shown as fractional polynomial prediction plots; shaded areas resemble 95% confidence intervals. In the graphs representing the MIHMoSA-study, all data from the outlier with exaggerated natriuresis were removed to enhance interpretability.

A possible explanation lies in the non-osmotic storage of sodium. This ingenious mechanism is still being elucidated but seems to assist mammals in limiting unrestrained fluid accumulation in conditions of extreme sodium loading. Indeed, several experiments suggest that significant amounts of sodium can be stored in an osmotically inactive form, which does not contribute to body fluid retention (Fig. 5) [25,26]. Depending on conditions that are not fully unraveled, the excess sodium is stored in the interstitial matrix of the skin, muscle and the endothelial surface layer, presumably bound to negatively charged glycosaminoglycans, as demonstrated in animal experiments and experiments in humans using magnetic resonance imaging of sodium (Na-MRI). [27-29] Captured in this large negatively charged capacitor, sodium does not exert an influence on total body water. This third space sodium storage is locally regulated by osmosensing immune cells via the tonicity-responsive enhancer binding protein TonEBP, inducing cellular and extracellular protection against osmotic stress [30]. Non-osmotic storage seems particularly relevant when dietary sodium intake is increased from average amounts to much higher levels [31]. Recent efforts to quantify non-osmotic storage showed that a significant amount of an intravenous sodium load can be osmotically inactivated [32].

It remains a matter of speculation whether non-osmotic storage of large amounts of sodium has a clinical impact during the acute care of patients. Possibly, positive sodium balances will lead to a prolonged, rather than increased fluid retention. In this view, large amounts of stored sodium would need to be released from their non-osmotic

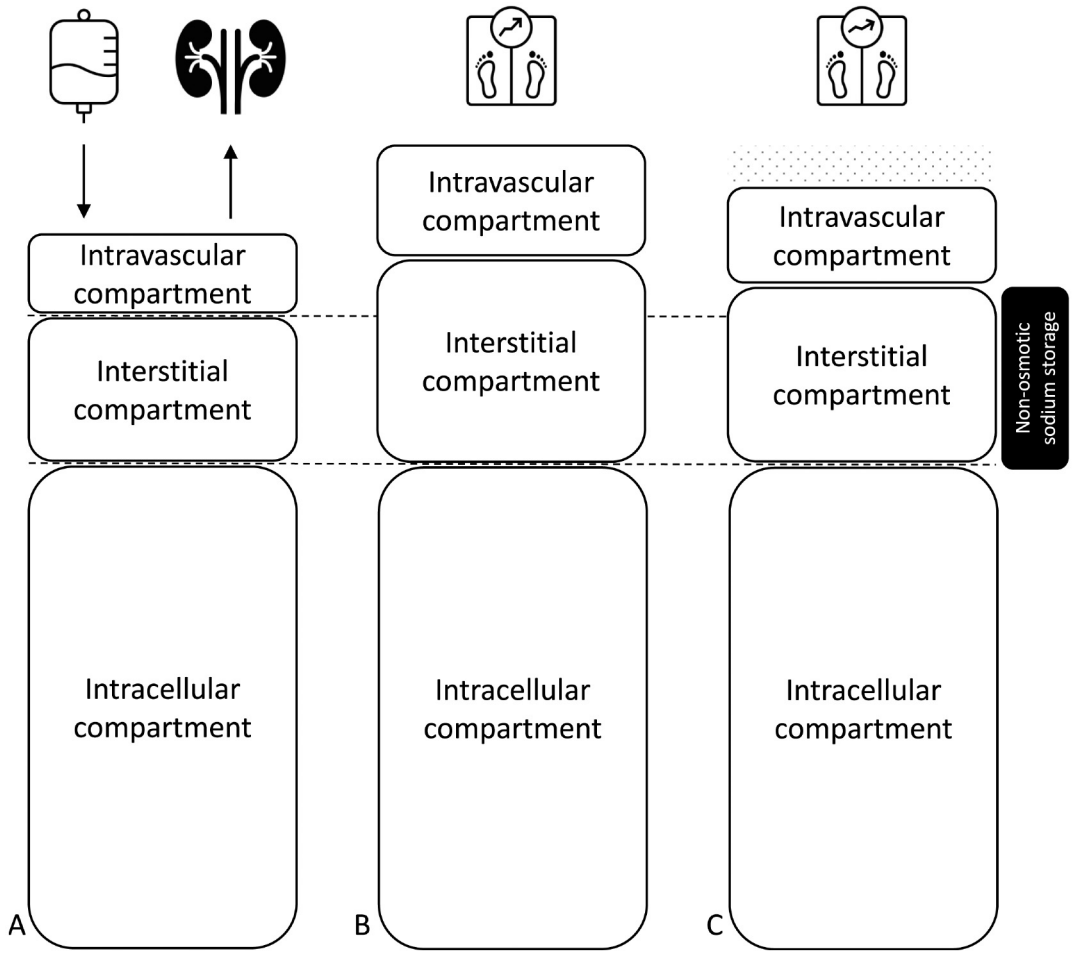

Fig. 5. Simplified illustration of the impact of non-osmotic sodium storage on fluid retention and changes in body weight after sodium administration. Panel A: Representation of the typical physiologic body fluid compartments (intracellular volume 2/3rd, extracellular volume 1/3rd which consists of interstitial volume 3/4th and intravascular volume 1/4th). Panel B: distribution of sodium and water after an isotonic fluid administration, according to the traditional theory. Of note, all sodium attracts/retains the same amount of water and electrolyte concentrations are equal in all compartments after equilibrium is reached. Panel C: distribution of sodium and water after an isotonic fluid administration according to a modern view, taking into consideration the osmotically inactive storage of (hypertonic) sodium in the interstitial tissue of skin, muscle, and the endothelial surface layer. The result is a higher renal clearance of water and thus a reduced weight gain after sodium administration. The dotted area represents the additional amount of water that has been excreted by the kidneys in this situation.

reservoirs to be excreted. Conceivably, this could take days or even weeks, even in the presence of a normal kidney function. Maybe, non-osmotic storage capacity could even play a role in the very common ICU acquired hypernatremia, that is observed even in the presence of positive fluid balances [33].

6. Conclusions

Starting from previous findings indicating that sodium-rich maintenance fluids lead to fluid retention, we now directly compared maintenance fluid treatment in two completely different settings. The ease with which sodium is excreted seems to depend on the difference between the amount of administered sodium and the subject's usual dietary intake in health, and, on top of that in the clinical setting, on the presence of reduced sodium excretion induced by intravascular hypovolemia. In a clinical setting, the latter process rapidly leads to a substantially positive sodium balance, itself causing a prolonged and presumably harmful fluid accumulation. The process of non-osmotic sodium storage could partially cope with this problem and avoid an abrupt and excessive fluid retention, but sodium and fluid accumulation will inevitably be prolonged. As the administration of superfluous sodium administration can be significantly and safely reduced by the use of low-sodium maintenance fluid therapy, we strongly suggest this approach when maintenance fluids are considered necessary.

Conflicts of interest

Dr. Van Regenmortel and Dr. Malbrain report speaker's fees from Baxter Belgium. Dr. Van Regenmortel was member on an advisory board on fluid therapy organised by Baxter (2017). Dr. Van Regenmortel and Dr. Malbrain are the chairmen of the International Fluid Academy, a non-profit organisation promoting education on fluid management and hemodynamic monitoring that received sponsoring from the industry (www.fluidacademy.org). The other authors have nothing to disclose.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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