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Incidence of hyperkalemia during hypertonic saline test for the diagnosis of diabetes insipidus

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Abstract

Objective: Hyperkalemia has been reported upon different hypertonic saline infusion protocols. Since hypertonic saline test has recently been validated for the differential diagnosis of diabetes insipidus (DI), we aimed to investigate the course of plasma potassium during the test.

Design: We analyzed data of 90 healthy volunteers and 141 patients with polyuria–polydipsia syndrome (PPS) from two prospective studies evaluating the hypertonic saline test. Our primary outcome was the incidence rate of hypertonic saline-induced hyperkalemia > 5 mmol/L.

Methods: Participants received a 250 mL bolus of 3% NaCl solution, followed by 0.15 mL/min/kg body weight continuously infused targeting a plasma sodium level of 150 mmol/L. Blood samples and clinical data were collected every 30 min.

Results: Of the 231 participants, 16% (*n* = 37/231) developed hyperkalemia. The incidence of hyperkalemia was higher in healthy volunteers and in patients with primary polydipsia (25.6% (*n* = 23/90) and 9.9% (*n* = 14/141), respectively), and only occurred in 3.4% (*n* = 2/59) of patients with diabetes insipidus. Hyperkalemia developed mostly at or after 90-min test duration (81.1%, *n* = 30/37). Predictors of hyperkalemia (OR (95% CI)) were male sex (2.9 (1.2–7.4), *P* = 0.02), a plasma potassium at baseline > 3.9 mmol/L (5.2 (1.8–17.3), *P* = 0.004), normonatremia at 30-min test duration (3.2 (1.2–9.5), *P* = 0.03), and an increase in potassium levels already at 30-min test duration as compared to baseline (4.5 (1.7–12.3), *P* = 0.003). Hyperkalemia was transient and resolved spontaneously in all cases.

Conclusion: The hypertonic saline test can lead to hyperkalemia, especially in patients with primary polydipsia who experience a longer test duration. Monitoring potassium levels in these patients is recommended.

Key Words

▶ potassium

▶ 3% NaCl

▶ polyuria–polydipsia syndrome

▶ PPS

Introduction

The hypertonic saline infusion test with continuous infusion of 3% NaCl has recently been put forward as a new test for the diagnosis of diabetes insipidus (DI) (1). For other indications such as hemorrhagic and septic shock, elevated intracranial pressure, correction of hyponatremia, and for fluid substitution during major operations, it has already been used since decades, with different concentrations and different infusion protocols (2, 3). In these contexts, electrolyte and acid-base imbalances following hypertonic saline infusion have been widely described. Specifically, a decrease from baseline plasma potassium levels soon after administration of a bolus (4, 5, 6) and an increase in plasma potassium levels up to the hyperkalemic range after continuous infusion of hypertonic saline (7, 8) have been reported. Patients with kidney failure seem to be at particular risk for developing hypertonic saline-induced hyperkalemia (9, 10). However, hyperkalemia during or after hypertonic saline infusion has also been described in patients with normal renal function (7). In a randomized, double-blind study in 14 women undergoing hysterectomy receiving a 10-min infusion of 4 mL/kg 7.5% saline, plasma potassium initially showed a minor decrease followed by a significant increase of up to 1.4 mmol/L above baseline over the next hour. This effect was not seen in matched women receiving the same amount of 0.9% saline infusion (7).

Due to the fact that all these studies used different infusion protocols and different doses of hypertonic saline, the incidence and clinical impact of hyperkalemia in association with hypertonic saline infusion remains unclear.

In view of the emerging role of hypertonic saline infusions for the differential diagnosis of DI (11), we aimed to investigate the course of plasma potassium levels during a standardized hypertonic saline infusion test with 3% saline in a large cohort of healthy volunteers and patients with polyuria–polydipsia syndrome (PPS). The primary aim of our study was to assess whether the 3% saline infusion test is associated with a risk of developing hyperkalemia and to define potential risk factors.

Material and methods

Study design and participants

This was a secondary analysis of previously collected data from two prospective studies: we analyzed data (1) from 90 healthy volunteers undergoing a hypertonic saline infusion test at two tertiary medical centers (University Hospital Basel, Switzerland and University Hospital of Wuerzburg, Germany) in 2012; (2) from 141 patients with the PPS undergoing osmotic stimulation with the hypertonic saline infusion test at 11 tertiary medical centers in Germany, Switzerland and Brazil from July 2013 to June 2017. Full details of the studies' rationales, designs and statistical analyses have been published elsewhere (1, 12). Both studies had been registered on ClinicalTrials.gov (NCT01940614/NCT02647736) and approved by local ethic committees, and this was a subanalysis of the data to assess the safety of the 3% NaCl test for the differential diagnosis of diabetes insipidus, originally approved by the ethic commission of the main center Basel (EKNZ, former EBB). In brief, healthy volunteers were of age 18 years or older, had a baseline sodium level 135–145 mmol/L, and a euvolemic status. Exclusion criteria included pregnancy, a history or presence of PPS, which comprises all forms of DI and primary polydipsia (PP), any chronic or therapy-requiring diseases, chronic alcohol consumption, or drug intake (except oral contraception), a BMI > 28 kg/m^2 or < 18 kg/m^2, a GFR < 60 mL/1.73 m^2, anemia of any grade, hypertension, and diabetes mellitus. Every healthy volunteer underwent a standardized clinical examination at baseline with evaluation of volemic state, measurement of blood pressure, heart rate, weight and height as well as blood sampling for measurement of plasma osmolality, sodium, potassium, glucose and creatinine, and urine sampling for measurement of urine osmolality. Eligible patients were of age 16 years or older with a confirmed diagnosis of central diabetes insipidus or with hypotonic polyuria, defined as a urine output of > 50 mL/kg of body weight during a 24-h period, and a urine osmolality < 800 mOsm/kg. Patients with nephrogenic diabetes insipidus were excluded from the study. Moreover, patients with glycosuria-induced polyuria, electrolyte disorders, untreated or insufficiently replaced pituitary-, adrenal- or thyroid deficiency or impaired kidney function, heart failure, uncontrolled hypertension or a history of epilepsy were ineligible. In addition, pregnancy or breastfeeding was an exclusion criterion.

Hypertonic saline infusion test protocol

The test protocol was the same for healthy volunteers and patients. All study participants refrained from smoking and drinking alcoholic beverages for at least 24 h prior to the test. No food intake was allowed after midnight, no fluid intake after 06:00 h on the test day. Participants underwent the hypertonic saline infusion test between

08:00 h and 11:00 h. Baseline blood measurement was taken after a 30-min rest in a recumbent position. The 3% saline infusion was administered as follows: participants received a 250 mL bolus, followed by 0.15 mL/min/kg body weight continuous infusion. The infusion was stopped after reaching a plasma sodium level of 150 mmol/L, later plasma sodium levels were quickly re-lowered via oral and parenteral rehydration. Blood samples for sodium, potassium, and osmolality measurement as well as clinical data were collected every 30 min during the hypertonic saline infusion as well as 30–60 min after test termination. Blood sampling took place from the contralateral arm rather than the 3% saline infusion arm, and blood analysis took place immediately after sampling.

Laboratory measurements

Potassium levels were available from either indirect or direct ion-selective (ISE) method, or both. During the hypertonic saline infusion test, additional direct ISE measurements were performed at each time point when hyperkalemia had occurred, in order to exclude false hyperkalemia due to pre-analytic or analytic problems. In these cases, only direct ISE-confirmed potassium levels > 5 mmol/L were included in the analysis.

Hyperkalemia was defined as a blood potassium level > 5 mmol/L. The grade of hyperkalemia was classified according to current practice into mild (5.1–5.5 mmol/L), moderate (5.6–6.0 mmol/L), and severe (>6.0 mmol/L) (13).

Blood samples were immediately transported to the central laboratory in standard biochemistry tubes. Lithium-heparin plasma tubes were centrifuged, and plasma potassium levels were analyzed by indirect ISE method (cobas® 8000 modular analyzer, Roche Diagnostics). Heparinized blood gas tubes were used to collect venous blood gas samples and potassium levels were measured by direct ISE method (ABL 800 Flex®, Radiometer GmbH, or ABL90 FLEX®, Radiometer GmbH). Plasma osmolality was measured in lithium-heparin plasma tubes using the freezing point method.

Outcomes

The primary outcome of this analysis was the percentage of participants developing hyperkalemia of any grade during the hypertonic saline infusion test. In addition, we aimed to show potassium course patterns during the hypertonic saline test and highlight factors associated with development of hyperkalemia during the test.

Statistical analysis

Data were analyzed using *R* software (14) Version 4.0.0 (2020-04-24). Baseline characteristics were described as percentage of participants, or mean ± s.d. if normally distributed, and median and interquartile range (IQR) if not. The analysis was performed for the whole group of participants as well as separately for healthy volunteers, patients with PP, and patients with central DI.

To compare the baseline characteristics of participants developing hyperkalemia vs participants who did not, a Wilcoxon test was used to assess differences between continuous variables and a chi square test or a Fisher's exact test for categorical variables. Box-plots were used to visualize the plasma potassium course during the test in a descriptive analysis of the participants.

We performed a multivariable analysis in order to identify which factors, present at baseline respectively at 30-min test duration, are associated with development of hyperkalemia later during the test. After performing a backward stepwise model selection, the following predictors were included in the model: age, sex, baseline plasma potassium > 3.9 mmol/L, normal plasma sodium level 30 min after test start, and dynamic of plasma potassium at 30-min test duration, defined as a binary variable according to whether plasma potassium at 30-min test duration was higher than at baseline or not. The cutoff of 3.9 mmol/L for baseline potassium was chosen according to the preexisting literature (15).

Finally, we conducted a separate descriptive analysis in the subgroup of PPS patients.

Results

Baseline characteristics

Baseline characteristics for the whole group of patients and healthy volunteers are summarized in Table 1. Participants (*n* = 231) were 60% (*n* = 138/231) female, had a mean (s.d.) age of 36 (13) years, and a mean BMI of 25 (5.6) kg/m². Median (IQR) baseline plasma potassium and sodium levels were 4 (3.8–4.2) mmol/L and 140 (139–142) mmol/L, respectively. Kidney function was normal in all the participants. Among the 141 patients with PPS, 58% (*n* = 82/141) had PP and 42% (*n* = 59/141) had central DI, with 23/59 patients had partial DI. Six out of 141 patients (4%) had cerebrovascular disease, 4/141 (3%) had cardiovascular disease, 34/141 (24%) had brain tumor (mostly pituitary tumor), 32 (23%) had psychiatric disorder, and 39 (28%) had anterior pituitary insufficiency. Thirty-four out of the 39 patients with anterior pituitary

Table 1 Baseline characteristics.

	Complete cohort	Healthy volunteers	Patients	
			Patients with DI	Patients with PP
n (%)	231 (100)	90 (39)	59 (41.8)	82 (58.2)
Age, years mean (s.d.)	36 (13)	31 (9)	44 (13)	35 (12)
Weight, kg mean (s.d.)	74 (17)	70 (12)	82 (21)	73 (19)
BMI, kg/m^2 mean (s.d.)	25 (5.6)	23 (2.7)	28.5 (6.8)	24.8 (6.0)
Sex (female), *n* (%)	138 (60)	45 (50)	38 (64)	55 (67)
Baseline blood pressure, mmHg	120/75 (110–130/67–80)	122/72 (115–129/67–80)	125/75 (113–132/70–85)	116/70 (105–128/65–80)
Baseline plasma potassium, mmol/L median (IQR)	4 (3.8–4.2)	4 (3.8–4.2)	4 (3.8–4.2)	4 (3.8–4.2)
Baseline plasma osmolality, mmol/L/kg median (IQR)	288 (282–294)	289 (281–295)	291 (286–296)	282 (282–289)
Baseline plasma sodium, mmol/L median (IQR)	140 (139–142)	139 (138–141)	142 (140–144)	141 (139–142)
Baseline plasma urea, mmol/L median (IQR)	3.8 (2.4–4.9)	4.7 (3.7–5.4)	2.6 (1.3–4.3)	3.5 (2.2–4.4)
Baseline urine osmolality, mmol/L/kg	364 (198–626)	680 (300–885)	228 (116–380)	408 (237–576)
Diuretics, *n* (%)	6 (2.6)	0 (0)	4 (6.8)	2 (2.4)
Corticosteroids, *n* (%)	34 (14.7)	0 (0)	30 (50.8)	4 (4.9)
Cardiovascular disease, *n* (%)	4 (1.7)	0 (0)	3 (5.1)	1 (1.2)
Cerebrovascular disease, *n* (%)	6 (2.6)	0 (0)	5 (10.2)	1 (1.2)
Renal failure, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders, *n* (%)	32 (13.8)	0 (0)	10 (16.9)	22 (26.8)
Brain tumor, *n* (%)	34 (14.7)	0 (0)	29 (49.1)	5 (6.1)
Anterior pituitary insufficiency, *n* (%)	39 (16.9)	0 (0)	37 (62.7)	2 (2.4)

Data are expressed in percentage of patients in case of dichotomic variables, in mean ± s.d. for normal distributed continuous variables, and in median IQR for not normal distributed continuous variables. Comorbidities, arterial hypertension, cardiovascular disease, cerebrovascular disease, neoplasia, psychiatric disorder.

DI, central diabetes insipidus; PP, primary polydipsia; IQR, interquartile range.

insufficiency had an insufficiency of corticotroph axis and were therefore receiving a corticosteroid therapy. Four patients with central DI (three with partial DI) received diuretic therapy against arterial hypertension.

Incidence of hyperkalemia

Overall, 37 out of 231 participants undergoing the hypertonic saline infusion test developed hyperkalemia, leading to an incidence rate of 16%. In 26 (70%) of those participants, hyperkalemia was mild (>5 and ≤5.5 mmol/L), in 9 (24%) it was moderate (>5.5 and ≤6 mmol/L), and in 2 (5%) it was severe (>6 mmol/L).

Figures 1 and 2 show the course of potassium levels of the complete cohort and in different subgroups according to the development and severity of hyperkalemia during the test. Altogether, ten participants (4.3%) developed a mild hypokalemia during the test (defined as a potassium

value between 3.0 and 3.4 mmol/L). None of them eventually developed hyperkalemia.

Hyperkalemia occurred in 81.1% of the cases at or after 90-min test duration (*n* = 30/37 patients) and only in one patient before 60-min test duration. All cases of hyperkalemia spontaneously resolved after the hypertonic saline infusion test was stopped and participants rehydrated, as displayed in Fig. 2B.

Predictors of hyperkalemia

In the multivariable analysis, predictors for development of hyperkalemia were male sex (OR 2.9, 95% CI 1.2–7.4, *P* = 0.02), a plasma potassium at baseline > 3.9 mmol/L (OR 5.2, 95% CI 1.8–17.3, *P* = 0.004), a plasma sodium < 146 mmol/L at 30-min test duration (OR 3.2, 95% CI 1.2–9.5, *P* = 0.03), and a higher potassium at 30-min
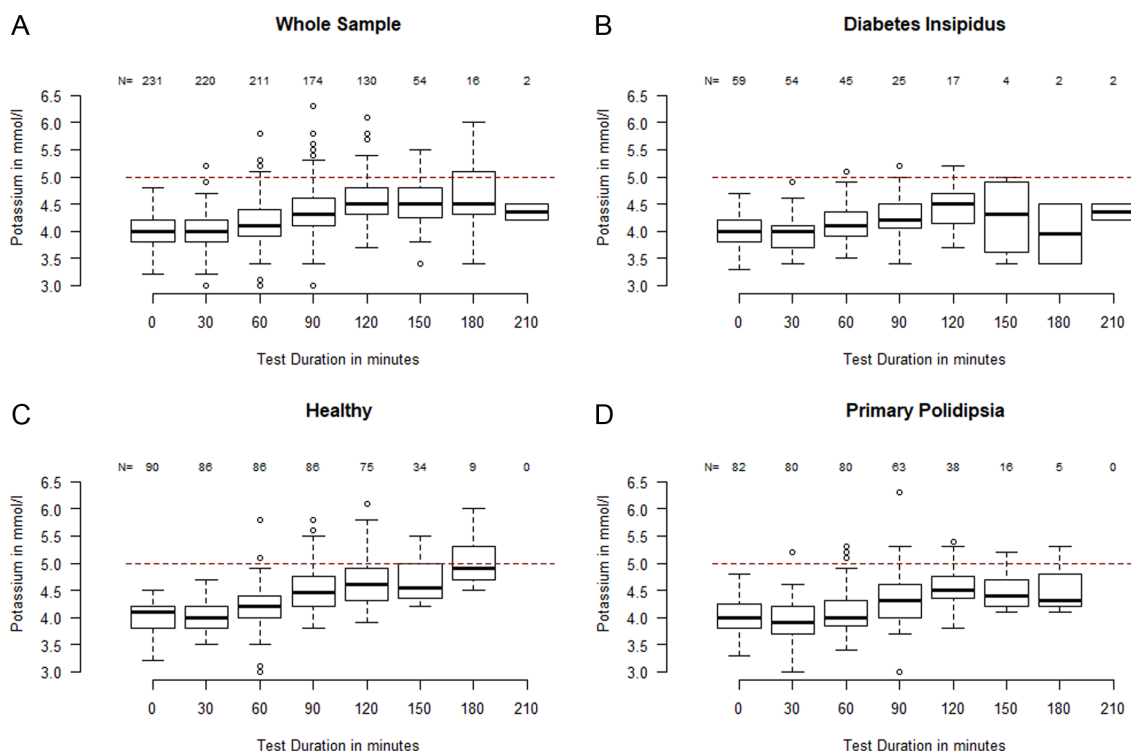
Figure 1
Plasma potassium course boxplots of plasma potassium course of (A) whole sample, (B) patients with diabetes insipidus, (C) healthy participants, and (D) patients with primary polydipsia. Potassium is measured in mmol/L, test duration in minutes; number of patients is reported above each boxplot. Boxes contain 50% of results (25–75% quartile, IQR), and the thick horizontal line is the median. The upper and lower whiskers represent results outside the middle 50% (1st quartile – 1.5*IQR resp. 3rd quartile + 1.5 IQR), the circles represent the outliers.

test duration than at baseline (OR 4.5, 95% CI 1.7–12.3, $P=0.003$) but not age (OR 0.96, 95% CI 0.91–1.00, $P=0.07$) (Table 2, Fig. 3).

Subanalysis of patients with PPS

In the subgroup of patients with PPS, incidence rates of hyperkalemia differed according to diagnosis, with 14.6% ($n=12/82$) in PP patients and 3.4% ($n=2/59$) in DI patients ($P=0.03$), both DI patients being diagnosed with a partial DI. There was no difference in baseline urea or glucose levels between DI and PP patients ($P=0.13$ resp. $P=0.20$).

The percentage of patients developing hyperkalemia was 7.5% ($n=7/93$) among female patients and 14.6% ($n=7/48$) among male patients ($P=0.23$). There was no age difference between patients developing and not developing hyperkalemia ($P=0.19$), and no difference in baseline plasma potassium ($P=0.34$), urea ($P=0.42$), or glucose levels ($P=0.12$).

PPS patients developing hyperkalemia had on average a longer test duration, with a median (IQR) of 120 (120–120) min vs 90 (60–120) min ($P=0.02$). In the majority of patients developing hyperkalemia (78.6%),

potassium levels increased already at 30-min test duration compared to baseline ($P < 0.01$), whereas it decreased in patients not developing hyperkalemia. Cardiovascular or cerebrovascular disease was present in 7% ($n=1/14$) of patients developing hyperkalemia and in 7% ($n=9/127$) not developing hyperkalemia ($P=1$). Treatment with corticosteroids was not associated with development of hyperkalemia ($P > 0.1$). None of the patients receiving diuretics developed hyperkalemia.

Discussion

Our study has the following main findings. First, hypertonic saline infusion in a protocol as it is proposed for the differential diagnosis of DI can lead to hyperkalemia, especially in patients with a test duration $\geq$ 90 min, which are mostly patients with PP. Secondly, risk factors for development of hyperkalemia for male sex are a high baseline potassium level, a slow increase in sodium levels during the test, and an increase in potassium level already at 30-minute test duration. Thirdly, hypertonic saline-induced hyperkalemia was mostly mild and
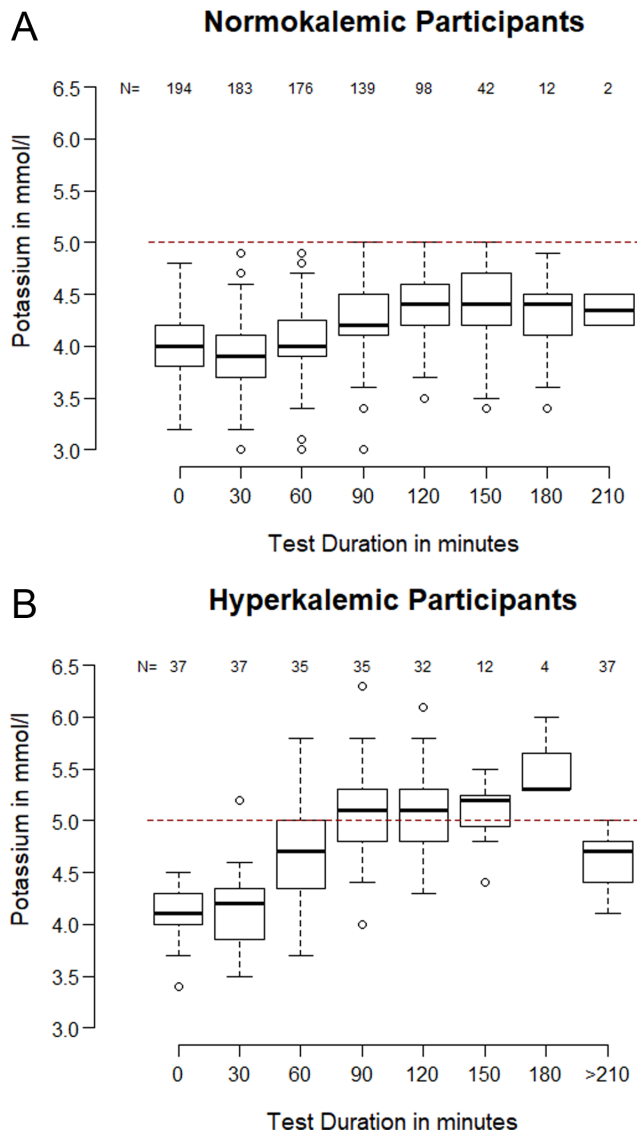
Figure 2
Normokalemic and hyperkalemic participants boxplots of plasma potassium course of normokalemic and hyperkalemic participants: (A) normokalemia (*n* = 214), (B) hyperkalemia (*n* = 37). Potassium is measured in mmol/L, test duration in minutes; number of patients (*n*) is reported above each boxplot. Boxes contain 50% of results (25–75% quartile), and the thick horizontal line is the median. The upper and lower whiskers represent results outside the middle 50% (1st Quartile – 1.5*IQR resp. 3rd quartile + 1.5 IQR), the circles represent the outliers.

resolved spontaneously at the end of the test protocol. Nevertheless, caution is needed in patients here showing the identified predictors for hyperkalemia.

With hypertonic saline infusion being proposed as the new standard test for the differential diagnosis of DI (11), it is important to clarify whether this test is leading to potentially harmful hyperkalemia, as previously described for other hypertonic saline infusion protocols.

In these reports, patients receiving hypertonic fluids during surgical operations (4, 7, 16) or for resuscitation (17) showed moderate to severe and in some cases symptomatic hyperkalemia, independent from infusion rate (18, 19).

In our study, 16% of participants developed hyperkalemia, with a higher percentage in patients with PP as compared to patients with DI. Moreover, only patients with partial DI developed hyperkalemia. This was primarily because test duration was strongly associated with development of hyperkalemia, which occurred in 81.1% of the cases at or after 90-min test duration, and patients with DI had on average a shorter test duration. Not surprisingly, in this context, a normal plasma sodium level at 30-min test duration was also associated with later development of hyperkalemia. In fact, this parameter has to be seen as a surrogate for a longer test duration, as the test is only stopped when a plasma sodium level ≥ 150 mmol/L is reached (1, 12).

Reassuringly, hyperkalemia was transient and resolved spontaneously and without sequelae soon after the infusion was stopped.

To identify patients at risk for hyperkalemia early, predictors already known at baseline would be of particular importance. Renal failure has been reported as a risk factor for development of hyperkalemia upon hypertonic saline infusions (10) due to the associated limited plasma potassium clearance (13). However, this was not applicable in our study since kidney function was normal in all participants. Other studies described male sex, age (20), and a baseline plasma potassium level higher than 3.9 mmol/L (15) as risk factors. Indeed, in our analysis, male sex and plasma potassium level at baseline were predictors for later hyperkalemia. In contrast, age was not associated with onset of hyperkalemia in the multivariable model. A possible explanation is that the average age in our cohort was 36 years, whereas in previous studies, older age was associated with the risk of hyperkalemia (20). Interestingly, the dynamic of plasma potassium levels already after the 250 mL bolus of hypertonic saline was a strong predictor for development of hyperkalemia. A transient decrease of plasma potassium following a bolus infusion of hypertonic saline has already been described (21). In our study, we only observed this transient initial potassium decrease in participants who stayed normokalemic. Whether participants developing hyperkalemia did not experience a drop in potassium levels or whether this drop occurred before 30-minute test duration cannot be clarified, as we do not have data about potassium levels between 0- and 30-min test duration.

Table 2 Multivariable model.

	Complete Cohort	Normokalemia	Hyperkalemia	OR	95% CI	P
Age, years mean (s.d.)	36.0 (12.7)	36.6 (12.9)	31.2 (8.7)	0.96	0.91–1.00	0.07
Sex (male), *n* (%)	93 (40.3)	70 (36.1)	23 (62.1)	**2.88**	**1.18–7.37**	**0.02**
Baseline plasma potassium > 3.9 mmol/L , *n* (%)	128 (55.4)	102 (52.6)	26 (70.3)	**5.20**	**1.82–17.29**	**0.004**
Plasma sodium at 30 min < 146 mmol/L, *n* (%)	123 (53.2)	93 (47.9)	30 (81.1)	**3.16**	**1.19–9.53**	**0.03**
Increase of plasma potassium at 30 min, *n* (%)	56 (24.2)	41 (21.1)	15 (40.5)	**4.48**	**1.71–12.3**	**0.003**

Number and characteristics of participants developing or not developing hyperkalemia. Data are expressed in percentage of patients in case of dichotomic variables, in mean ± s.d. for normal distributed continuous variables. Predictors of hyperkalemia at baseline and at 30-min test duration. Results of multivariable logistic regression model with hyperkalemia as dependent variable. Bold indicates statistical significance, *P* < 0.05. OR, odds ratio.

Different mechanisms have been suggested to explain how hypertonic saline might influence plasma potassium levels. Some studies report the possible role of an osmotic drive ('solvent drag') in sodium/potassium balance, supported by findings of hyperkalemia in patients receiving hypertonic solutions such as mannitol or radiocontrast medium (16, 22, 23, 24). Early pathophysiological studies suggest an intracellular fluid (ICF) potassium and other ions uptake as an early compensatory mechanism to increase the intracellular osmolality and balance the hyperosmolar-induced cell shrinkage (8, 25). Since ions' accumulation alter the cell membrane, it represents only a temporary solution for the cell (26), and a relative, transient hyperkalemia may occur once water enters the cell, organic osmolytes (e.g. glutamine and other aminoacids, glutamate, taurine, myo-inositol, etc.) are synthetized or shifted into ICF, and the previously internalized potassium is released back to extracellular fluid (ECF). As adaption to a chronic hyperosmolar state, DI patients might have a different ion and organic osmolyte balance at baseline (27, 28), generating a different potassium shift in response to a hyperosmolar challenge as compared to PP or healthy volunteers. Other studies suggest that hypertonic
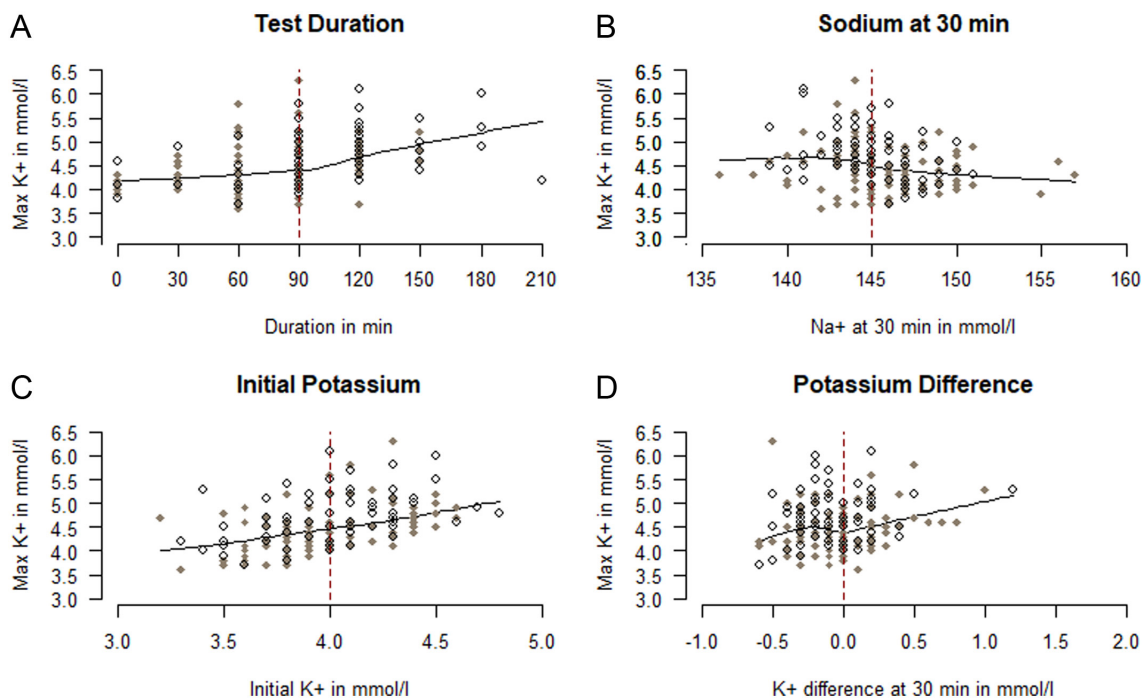

Figure 3
Predictors and potassium levels: distribution of the sample according to maximal potassium level and (A) test duration, (B) sodium level at 30-min test duration, (C) initial potassium level, and (D) potassium difference at 30-min test duration. Gray represents female participants and black represents the males.

saline-induced hyperchloremic metabolic acidosis to be responsible for a potassium shift from ICF to ECF (29, 30). Some other studies (10, 31, 32, 33) propose a renal adaptation mechanism through the renin/aldosterone system to be responsible for hyperkalemia. Considering the fast dynamic of electrolyte changes, an ICF/ECF shifting seems more likely than a renal adaptation as explanation for the transient hyperkalemia.

One could argue that hyperkalemia may be just the result of hemolysis following hypertonic infusion or a pre-analytical problem. However, as showed by Garcia *et al.* in 2009, infusion of hypertonic saline solution only induces hemolysis when saline concentration is ≥ 7.02%, whereas this effect is not found with saline solutions between 0.41 and 4.68% (34). Moreover, we double-checked hyperkalemia performing blood gas analyses and confirmed only hyperkalemias were included in our analysis.

Unfortunately, as it was a secondary analysis of previously collected data, we do not have detailed parameters for highlighting pathophysiological mechanisms of hypertonic saline-induced hyperkalemia. We did not collect data about aldosterone or organic osmolytes and had only limited data about pH levels and chloride. We can therefore only speculate on the mechanisms of changes in potassium levels upon hypertonic saline infusion. In addition, the number of events was not sufficient to allow separate multivariable analysis, neither in the subgroups of patients and healthy volunteers nor in the subgroup of patients with and without comorbidities or diuretic therapy. Due to the sample size, it is difficult to extrapolate information on whether duration and cause of PPS may influence the incidence of hyperkalemia. Moreover, our results are difficult to be generalized to a more multi-morbid cohort who may be on medications such as antihypertensive drugs, which may affect renal potassium handling. Nevertheless, since this is the largest cohort of PPS patients undergoing the same protocol of hypertonic infusion, in our opinion, it is representable in everyday clinical practice for patients undergoing this test.

In conclusion, the hypertonic saline infusion test using the protocol proposed for differential diagnosis of DI can lead to hyperkalemia, especially in patients with PP in whom a longer test duration is usually needed. Male sex, a plasma potassium level > 3.9 mmol/L at baseline, an increase of plasma potassium 30 min after hypertonic saline bolus and a normal plasma sodium at 30-min test duration help identifying patients at risk of developing hyperkalemia during the test. Even though in our cohort

hypertonic saline test-induced hyperkalemia was resolved spontaneously without clinical symptoms, caution is needed and we recommend to carefully monitor potassium levels in patients showing the previously described characteristics.

References

1 Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira A, Drescher T, Bilz S, Vogt DR, *et al.* A copeptin-based approach in the diagnosis of diabetes insipidus. *New England Journal of Medicine* 2018 **379** 428–439. (https://doi.org/10.1056/NEJMoa1803760)

2 Rizoli SB, Rhind SG, Shek PN, Inaba K, Filips D, Tien H, Brenneman F & Rotstein O. The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. *Annals of Surgery* 2006 **243** 47–57. (https://doi.org/10.1097/01.sla.0000193608.93127.b1)

3 Jensen JM, Mose FH, Bech JN, Nielsen S & Pedersen EB. Effect of volume expansion with hypertonic- and isotonic saline and isotonic glucose on sodium and water transport in the principal cells in the kidney. *BMC Nephrology* 2013 **14** 202. (https://doi.org/10.1186/1471-2369-14-202)

4 Bender R, Breil M, Heister U, Dahmen A, Hoeft A, Krep H & Fischer M. Hypertonic saline during CPR: feasibility and safety of a new protocol of fluid management during resuscitation. *Resuscitation* 2007 **72** 74–81. (https://doi.org/10.1016/j.resuscitation.2006.05.019)

5 Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, Kincaid MS, Britz GW & Lam AM. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology* 2007 **107** 697–704. (https://doi.org/10.1097/01.anes.0000286980.92759.94)

6 Ayach T, Nappo RW, Paugh-Miller JL & Ross EA. Postoperative hyperkalemia. *European Journal of Internal Medicine* 2015 **26** 106–111. (https://doi.org/10.1016/j.ejim.2015.01.010)

7 Kolsen-Petersen JA, Nielsen JOD & Tonnesen E. Acid base and electrolyte changes after hypertonic saline (7.5%) infusion: a randomized controlled clinical trial. *Scandinavian Journal of Clinical and Laboratory Investigation* 2005 **65** 13–22. (https://doi.org/10.1080/00365510410003138)

8 Todd MM. Hyperosmolar therapy and the brain: a hundred years of hard-earned lessons. *Anesthesiology* 2013 **118** 777–779. (https://doi.org/10.1097/ALN.0b013e3182815980)

9 O'Malley CMN, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS & Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesthesia and Analgesia* 2005 **100** 1518–1524. (https://doi.org/10.1213/01.ANE.0000150939.28904.81)

10 Conte G, Dal Canton A, Imperatore P, De Nicola L, Gigliotti G, Pisanti N, Memoli B, Fuiano G, Esposito C & Andreucci VE. Acute increase in plasma osmolality as a cause of hyperkalemia in patients with renal failure. *Kidney International* 1990 **38** 301–307. (https://doi.org/10.1038/ki.1990.200)

11 Rosen CJ & Ingelfinger JR. A reliable diagnostic test for hypotonic polyuria. *New England Journal of Medicine* 2018 **379** 483–484. (https://doi.org/10.1056/NEJMe1808195)

12 Fenske WK, Schnyder I, Koch G, Walti C, Pfister M, Kopp P, Fassnacht M, Strauss K & Christ-Crain M. Release and decay kinetics of copeptin vs AVP in response to osmotic alterations in healthy volunteers. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 505–513. (https://doi.org/10.1210/jc.2017-01891)

13 Lehnhardt A & Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. *Pediatric Nephrology* 2011 **26** 377–384. (https://doi.org/10.1007/s00467-010-1699-3)

14 R Core Development Team. R: a language and environment for statistical computing, 3.2.1, 2015. (available at: https://www.r-project.org/)

15 Song YH, Cai GY, Xiao YF, Wang YP, Yang ST & Chen XM. Can we predict who will develop postoperative hyperkalaemia after parathyroidectomy in dialysis patients with secondary hyperparathyroidism? *BMC Nephrology* 2019 **20** 225. (https://doi.org/10.1186/s12882-019-1416-9)

16 Fanous AA, Tick RC, Gu EY & Fenstermaker RA. Life-threatening mannitol-induced hyperkalemia in neurosurgical patients. *World Neurosurgery* 2016 **91** 672.e5–672.e9. (https://doi.org/10.1016/j.wneu.2016.04.021)

17 Seto A, Murakami M, Fukuyama H, Niijima K, Aoyama K, Takenaka I & Kadoya T. Ventricular tachycardia caused by hyperkalemia after administration of hypertonic mannitol. *Anesthesiology* 2000 **93** 1359–1361. (https://doi.org/10.1097/00000542-200011000-00036)

18 Hirota K, Hara T, Hosoi S, Sasaki Y, Hara Y & Adachi T. Two cases of hyperkalemia after administration of hypertonic mannitol during craniotomy. *Journal of Anesthesia* 2005 **19** 75–77. (https://doi.org/10.1007/s00540-004-0270-4)

19 Flynn BC. Hyperkalemic cardiac arrest with hypertonic mannitol infusion: the strong ion difference revisited. *Anesthesia and Analgesia* 2007 **104** 225–226. (https://doi.org/10.1213/01.ane.0000249801.01029.55)

20 Hunter RW & Bailey MA. Hyperkalemia: pathophysiology, risk factors and consequences. *Nephrology, Dialysis, Transplantation* 2019 **34** (Supplement 3) iii2–iii11. (https://doi.org/10.1093/ndt/gfz206)

21 García-Palmieri MR. Reversal of hyperkalemic cardiotoxicity with hypertonic saline. *American Heart Journal* 1962 **64** 483–488. (https://doi.org/10.1016/0002-8703(62)90033-9)

22 Rado JP. Effect of pharmacological doses of aldosterone on the hyperosmolality induced hyperkalemia. *Hormone and Metabolic Research* 1977 **9** 251. (https://doi.org/10.1055/s-0028-1095562)

23 Hayakawa K, Nakamura T & Shimizu Y. Role of hemolysis in potassium release by iodinated contrast medium. *European Radiology* 1999 **9** 1357–1361. (https://doi.org/10.1007/s003300050848)

24 Manninen PH, Lam AM, Gelb AW & Brown SC. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. *Canadian Journal of Anaesthesia* 1987 **34** 442–446. (https://doi.org/10.1007/BF03014345)

25 McManus ML, Churchwell KB & Strange K. Regulation of cell volume in health and disease. *New England Journal of Medicine* 1995 **333** 1260–1266. (https://doi.org/10.1056/NEJM199511093331906)

26 Strange K. Cellular volume homeostasis. *Advances in Physiology Education* 2004 **28** 155–159. (https://doi.org/10.1152/advan.00034.2004)

27 Gullans SR & Verbalis JG. Control of brain volume during hyperosmolar and hypoosmolar conditions. *Annual Review of Medicine* 1993 **44** 289–301. (https://doi.org/10.1146/annurev.me.44.020193.001445)

28 Delpire E & Gagnon KB. Water homeostasis and cell volume maintenance and regulation. *Current Topics in Membranes* 2018 **81** 3–52. (https://doi.org/10.1016/bs.ctm.2018.08.001)

29 Commereuc M, Nevoret C, Radermacher P, Katsahian S, Asfar P, Schortgen F & HYPER2S Investigators. Hyperchloremia is not associated with AKI or death in septic shock patients: results of a post hoc analysis of the 'HYPER2S' trial. *Annals of Intensive Care* 2019 **9** 95. (https://doi.org/10.1186/s13613-019-0570-3)

30 Rieder M, Hansford M, Stun L & Braksick S. 887: Incidence of hyperchloremia and acute kidney injury associated with hypertonic saline administration. *Critical Care Medicine* 2020 **48** 423. (https://doi.org/10.1097/01.ccm.0000631684.76215.6b)

31 Wade JB, Stanton BA, Field MJ, Kashgarian M & Giebisch G. Morphological and physiological responses to aldosterone: time course and sodium dependence. *American Journal of Physiology: Renal Fluid and Electrolyte Physiology* 1990 **259** 28. (https://doi.org/10.1152/ajprenal.1990.259.1.F88)

32 Antaraki A, Rangou D & Chlouverakis C. The renin-aldosterone axis in patients with diabetes insipidus. *Clinical Endocrinology* 1994 **40** 505–510. (https://doi.org/10.1111/j.1365-2265.1994.tb02490.x)

33 Schalekamp MA, Donker SC, Jansen-Goemans A, Fawzi TD & Muller A. Dissociation of renin and aldosterone during dehydration: studies in a case of diabetes insipidus and adipsia. *Journal of Clinical Endocrinology and Metabolism* 1976 **43** 287–294. (https://doi.org/10.1210/jcem-43-2-287)

34 García Mario J & Ardila A. Cell volume variation under different concentrations of saline solution (NaCl). *Investigación Básica* 2009 **37** 101–105. (available at: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-33472009000200002&lng=en)