Original Article

Significance of hypernatremia due to SARS-CoV-2 associated ARDS in critically ill patients

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ABSTRACT

Background and Objectives: SARS-CoV-2-induced ARDS is a new entity that should be characterized as it appears to be different from standard ARDS. Hypernatremia is a biological alteration that seems to occur very often in this population without any clear cause. The present study aims to clarify the possible causes of hypernatremia and evaluate its impact on patient outcome. **Patients and Methods:** We conducted a retrospective one-day prevalence study in 2 intensive care units, which only treated COVID-19 patients with moderate to severe ARDS. We measured blood and urine electrolytes in all the patients. Patients with chronic renal failure or renal replacement therapy were excluded from the study. Hypernatremia was defined as plasma sodium levels above 145 mmol/L. **Results:** Inclusion criteria were met in 17 out of 24 patients. Hypernatremia was present in 52% patients. All had a natriuresis higher than 20 mmol/L and a urine osmolality above 600 mOsm/L. Hypernatremia was acquired in ICU as all the patients had a normal serum sodium level at admission. **Conclusion:** The incidence of hypernatremia was elevated and appears to be linked to significant insensible water losses. This should trigger us to optimize the maintenance fluid therapy in critically ill patients with SARS-CoV-2-induced ARDS.

Key words: SARS-CoV-2, hypernatremia, COVID-19, insensible water losses

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BACKGROUND

Hypernatremia, defined by a plasma sodium concentration higher than 145 mmol/L,[1] is common in intensive care patients and may develop during the hospital stay.[2] Hypernatremia can be acquired either following excessively high sodium intake, loss of free water or a combination of the two.[3] The prevalence of hypernatremia in critically ill patients varies, ranging from 10% to 26%.[4–7] Acute respiratory distress syndrome (ARDS) is an independent factor associated with hypernatremia[8] and hypernatremia is an independent factor of intensive care unit (ICU) mortality.[5,6,8,9] A multi-center study of 7,067 patients showed that correction of hypernatremia on day 3 improved the survival of patients in ICU.[9] During the current SARS-CoV-2 epidemic, there appears to be an increased incidence of hypernatremia and renal failure in patients who require intensive care. The purpose of the present study was to characterize hypernatremia in this setting and determining its prevalence and its physiopathology.

PATIENTS AND METHODS

Patients

We carried out a retrospective one-day prevalence study in 2 intensive care units, which only treated SARS-CoV-2-induced ARDS patients. The urine electrolytes of our patients were analyzed routinely once a week. We included all the COVID-19 patients with ARDS criteria based on the thoracic CT scanner findings (number of abnormal pulmonary lobes and percent of affected parenchyma) associated with a positive SARS-CoV-2 antigen or PCR

on nasopharyngeal swab or broncho-alveolar lavage. We excluded patients with preexisting chronic renal failure and patients on renal replacement therapy.

Definitions of hypernatremia

Hypernatremia is defined as mild, moderate or severe according to a plasma sodium concentration above 145, 150, and 155 mmol/L respectively.[1,10] Borderline hypernatremia has been defined as serum sodium concentration between 143 and 145.[10] Dysnatremia is common at intensive care unit (ICU) admission. Mild to severe hypernatremia has been reported in 7.8% of the critically ill patients.[10] Mild hypernatremia (plasma sodium concentration >145 mmol/L) has been independently significantly associated with poor outcome.[10] In this study, we defined hypernatremia as a plasma sodium level >145 mmol/L.

Variables

After institutional ethics committee approval (BE 2020/82), we collected the basic patient demographics (age, sex, weight, body surface area), SAPS III score at admission and ARDS characteristics (number of affected lobes, percent of altered pulmonary parenchyma on thoracic CT scanner, PaO_2/FiO_2 ratio). We also recorded laboratory variables such as complete blood count, blood and urine chemistry on a spot urine, and arterial blood gases. We collected the cumulative water balance at the time of the blood and urine tests, the total water intake and the diuresis of the last 24 hours. Maximum plasma sodium concentration during the ICU stay was our criterion for creating the two patient populations (≤145 mmol/L and >145 mmol/L).

Statistics

The data were analyzed via Graphpad Prism 8 for Windows (GraphPad Software, La Jolla, California, USA) with a significance level of P <0.05. The normality of the distribution was tested by a Kolmogorov-Smirnov test. A Student's t-test was performed on the parametric variables and a Mann-Whitney test on non-parametric variables. Parametric variables are expressed as an average with standard deviation. Non-categorical variables are expressed as median with interquartile [25%–75%].

RESULTS

There were 24 patients in the two units on the day of the data collection. Seventeen patients were included in our study and 7 were excluded for preexisting chronic renal failure or renal replacement therapy.

According to the serum sodium levels, there were 9 patients in the hypernatremia group (serum Na >145 mmol/L) and 8 in the control group (serum Na ≤145 mmol/L). We

noted a male predominance in the hypernatremia group and in the study population as a whole (as has already been reported in Covid-19 disease[11,12]). The patients had similar SAPS III scores, the same number of pulmonary lobes affected on thoracic CT imaging and the same PaO_2/FiO_2 ratio. ICU length of stay was not significantly different between the groups. However, the body surface area was statistically larger in the hypernatremia group. Metabolic alkalosis seemed more compensated in the hypernatremia group than in the control group without any situation of permissive hypercapnia (Table 1).

Serum urea and creatinine were significantly higher in the hypernatremia group. The patients in the hypernatremia group also had a significantly higher bicarbonate level and plasma osmolarity. Serum sodium level was higher in the hypernatremia group (per definition), as were the maximal serum sodium levels during the ICU stay (P <0.0007). Interestingly, admission serum sodium level was normal and not different between the two groups. Serum osmolarity was significantly higher in the hypernatremia group whereas urine osmolality was not different between the groups and was above 600 mOsm/L. Urinary sodium was high in both groups. The sodium to creatinine ratio was higher in the control group (197 ± 143 *vs.* 86 ± 67, P = 0.05). The excretion fraction and U/B ratio tests were identical in the two groups.

The cumulative water balance was statistically identical, namely 3106 ± 22 *vs.* 2029 ± 1483 mL/ m² (P = 0.26) between the hypernatremic patients and the normonatremic patients. The same thing was observed concerning the daily diuresis 25.9 ± 6.1 *vs.* 27.8 ± 13.4 mL/kg/day (P = 0.71).

DISCUSSION

We are dealing with two populations of ARDS with COVID-19 of the same severity with a statistically identical PaO2/FiO2 ratio 105 ± 29 *vs.* 121 ± 34 (P = 0.32) and the same percentage of parenchyma diseased at CT 54 ± 22 *vs.* 40 ± 13% (P = 0.13) (Table 1). However, we observed a 52% incidence of acquired hypernatremia. Serum sodium levels measured on admission to the intensive care unit were below 145 mmol/L in all of the patients. A study of 8,142 consecutive patients in an intensive care unit over a 6-year period showed an incidence of acquired hypernatremia of 26%.[7] This phenomenon therefore seems particularly marked in the COVID-19 patients we studied. As in the study cited above, we observed a greater degree of renal failure, with creatinine 0.98 ± 0.36 in the hypernatremia group *vs.* 0.51 ± 0.13 in the control group (P = 0.003). A retrospective series of the first hospitalized patients in Wuhan, including 41 patients of which 16 were admitted to intensive care, showed that 15% of the patients admitted to

Table 1: Demographic general data of the population on sampling day

Variable	Population	Na >145	Na ≤145	P value
	n = 17	*n* = 9	*n* = 8	
Age - yr.	59 ± 14	58 ± 11	60 ± 18	0.80
Weight - kg	86 ± 15	92 ± 17	79 ± 9	0.08
Sex M- no. (%)	13 (76)	9 (100)	4 (50)	0.02
SAPS III score	43 ± 9	43 ± 9	44 ± 12	0.91
Affected lobes - no.	5 [5–5]	5 [4.5–5]	5 [5–5]	0.47
Lesions area - %	47 ± 19	54 ± 22	40 ± 13	0.12
PaO_2/FiO_2 ratio	113 ± 31	105 ± 29	121 ± 34	0.32
Length of stay, d	9 ± 4.7	10.3 ± 5.8	7.5 ± 3.1	0.23
Body surface area, m²	2.05 ± 0.20	2.15 ± 0.22	1.95 ± 0.12	0.03
pH	7.44 ± 0.06	7.41 ± 0.07	7.47 ± 0.02	0.03
$PaCO_2$ - mmHg	43 ± 12	49 ± 14	36 ± 5	0.03
PaO_2 - mmHg	76 ± 14	80 ± 14	71 ± 13	0.21
HCO_3^- - mmol/L	28 ± 3.5	29 ± 4	27 ± 2	0.14
Base excess	4 ± 2.7	4.6 ± 3.0	3.4 ± 2.3	0.38
Lactate – mmol/L	1.19 ± 0.45	1.30 ± 0.54	1.0 ± 0.3	0.30

SAPS: simplified acute physiology score

Table 2: Plasma electrolytes on sampling day

Variable	Population	Na >145	Na ≤145	P value
	n = 17	*n* = 9	*n* = 8	
Urea - mg/dL	55 ± 35	78 ± 33	30 ± 13	0.017
Creatinine - mg/dL	0.76 ± 0.36	0.98 ± 0.36	0.51 ± 0.13	0.003
Na - mmol/L	142 ± 9	147 ± 9.8	136 ± 3.1	0.007
K - mmol/L	4.2 ± 0.5	4.3 ± 0.7	4.1 ± 0.2	0.50
Cl - mmol/L	103 ± 7	107 ± 8.4	99 ± 3.6	0.01
HCO_3^- - mmol/L	26 ± 4	28 ± 4.7	23 ± 2.2	0.04
Albumin g/L	27 ± 3.7	28 ± 4.2	26 ± 2.9	0.26
Osmolarity mOsm/L	308 ± 25	323 ± 25	291 ± 11	0.005
Admission Na - mmol/L	138 [135–144]	137 [135–144]	139 [134–143]	0.52
Highest Na - mmol/L	147 ± 8.1	153 ± 7.3	141 ± 2.6	0.0007

intensive care had a creatinine higher than 1.5 mg/dL.[11] A second retrospective study including 138 patients showed a significant difference in the level of serum creatinine in patients admitted to intensive care versus those not admitted (80 [66–106] *vs.* 71 [58–84] μmol/L, *P* = 0.04).[12]

Urine osmolarity was greater than 600 mOsm/L in all patients. Patients appeared clinically euvolemic, even with a cumulative fluid balance of 9880 ± 3978 ml in hypernatremia patients and 3928 ± 2781 mL in controls, *P* = 0.10). This could mean significant insensible water losses[13] particularly since we observed a larger body surface area in the patients with hypernatremia (2.15 ± 0.22 *vs.* 1.95 ± 0.12 m², *P* = 0.03). Insensible losses are mainly respiratory or cutaneous. During mechanical ventilation, the upper airway is bypassed by orotracheal intubation and thus cannot contribute to the natural heat and moisture exchange process of inspired gases.[14] At low levels of inspired humidity, such as occurs with the delivery of medical gases, water is removed from mucous and the periciliary fluid by evaporation, causing insensible water losses.[14] Respiratory loss is minimized by the use of a heated humidifier in the ventilator circuits or HME filters. Other insensible losses are difficult to assess.

They are generally 14 ml/kg/day with an increase of 3 to 5 mL/kg/day per degree Celsius in the case of fever.[15] COVID-19 patients have persistent fever for up to 10 days and they can also have diarrhea, which is present in 16% of cases, and anorexia, present in 66% of cases, and diminution of thirst, which decreases spontaneous fluid intake by patients before admission.[12]

Median fluid intake of our patients was below 30 mL/kg/day without the need for iterative filling. Literature from postoperative care of thoracic surgery patients recommends not to exceed 1–2 mL/kg/h of maintenance fluids in order to avoid the risk of ARDS.[16] The total population of our study had daily intakes calculated at 1.1 mL/kg/h. It is also recommended not to exceed the daily positive fluid balance of 1500 mL/day.[16] In our patient population, there was a daily balance of 697 ± 880 ml. These values are at the lower level of the recommendations based on the experience of thoracic surgery. It is also recommended to pay attention to silent hypovolemia, which is a lack of water intake without immediate clinical repercussions. Silent hypovolemia can occur in situations such as coma and mechanical ventilation.[17]

Table 3: Urine electrolytes on sampling day

Variable	Population	Na >145	Na ≤145	P value
	n = 17	*n* = 9	*n* = 8	
Urea - mg/dL	2036 ± 732	2344 ± 545	1689 ±791	0.06
Creatinine - mg/dL	86 [49–108]	88 [64–108]	49 [41–109]	0.20
Na - mmol/L	89 [62–100]	84 [14–97]	92 [74–123]	0.33
Na/Creatinine ratio	138 ± 120	86 ± 67	197 ± 143	0.05
K - mmol/L	38 ± 17	36 ± 17	41 ± 17	0.59
K/Creatinine ratio	57 ± 32	50 ± 25	65 ± 39	0.34
Albumin g/L	50 [28–84]	66 [49–156]	67 [5–118]	0.58
Albumin/Creatinine ratio	81 [33–143]	81 [63–134]	75 [12–143]	0.66
Proteins g/L	0.51 [0.29-1.16]	0.51 [0.43–1.13]	0.44 [0.14–1.16]	0.50
Protein/Creatinine ratio	0.55 [0.46–1.52]	0.82 [0.46–1.0]	0.54 [0.25–1.0]	0.69
Osmolarity - mOsm/L	640 ± 176	673 ± 183	603 ± 173	0.43
Na EF	0.55 ± 0.35	0.47 ± 0.33	0.66 ± 0.38	0.32
Urea EF	38 ± 11	35 ± 12	42 ± 10	0.27
U/S Osmole	2.0 ± 0.61	2.1 ± 0.66	2.0 ± 0.60	0.91
Na/K ratio	1.9 [1.13–3.78]	1.6 [0.3–3.3]	2.5 [1.5–4.3]	0.32
U/P Creatinine ratio	99 [68–166]	73 [66–136]	139 [91–358]	0.23
U/P Urea ratio	48 ± 30	35 ± 17	62 ± 35	0.06
Urea/Creatinine ratio	73 ± 31	85 ± 30	60 ± 28	0.09

EF: excretion fraction; U: urine; P: plasma

Table 4: Fluid balance from ICU admission to sampling day

Variable	Population	Na >145	Na ≤145	P value
	n = 17	*n* = 9	*n* = 8	
FB daily	697 ± 880	765.7 ± 1159	620.1 ± 472.2	0.74
Diuresis - mL	1716 ± 687	1611 ± 293	1822 ± 949	0.55
DM - mL/kg/d	26.8 ± 9.9	25.9 ± 6.1	27.8 ± 13.4	0.71
DM - mL/m²/d	1044 ± 458	987 ± 445	1106 ± 494	0.61
FB cumulated - mL	5491 ± 3688	9880 ± 3978	3928 ± 2781	0 .10
FB/kg	66 ± 46	79 ± 50	50.92 ± 37.82	0.21
FB/m²	2599 ± 1934	3106 ± 2224	2029 ± 1483	0.26

DM: daily maintenance fluids; FB: fluid balance

The intensive care community is facing a different model of ARDS. In a study comparing two fluid-management strategies in acute lung injury (Fluid And Catheter Treatment Trial - FACTT), one third of the patients were on vasopressor support.[18] In our series, only one patient received norepinephrine, and only for two days. This low incidence of shock in our series seems unusual considering the series of 138 patients from Wuhan where 33 patients were hospitalized in the ICU with 22 patients (66%) in ARDS and 11 patients (33%) in shock.[12] There was no data on the number of patients having both ARDS and shock.[12] However, in the FACTT study, the cumulative water balance was negative –136 ± 491 mL in their conservative group and they did not observe more renal failure (5.5% ± 0.1% *vs.* 5.6% ± 0.1%, *P* = 0.45). The FACTT study did not provide us information on the patient's state of hydration or serum sodium levels, despite the fact that they combined several risk factors for hypernatremia, namely ARDS, septic shock, coma, bladder catheters and central catheters and the use of vasoactive drugs, steroids and antimicrobials.[8] Our study has shown that it is possible to have free water loss associated with hypernatremia and a positive fluid balance. Since the median admission serum sodium levels were well beneath 145 mmol/L, we can postulate that

overly restrictive ICU fluid intakes may lead to dehydration, which in our study was present in 52% of the patients with ARDS due to SARS-CoV-2.

All the patients had a natriuresis above 20 mmol/L and this could mean that sodium intake might also contribute to elevated plasma sodium. However, there was no significant difference between the two groups in terms of natriuresis (84 [14–97] *vs.* 92 [74–123] mmol/L, *P* = 0.33) in the hypernatremia group and the normonatremia group. However, it has been shown that 90% of the sodium consumed (from all sources) is excreted in urine.[19] This value is valid for 24 h urine samples. To get around this potential bias, we looked at the sodium to creatinine ratio and observed a lower ratio in patients with hypernatremia (86 ± 67 *vs.* 197 ± 143, *P* = 0.05) as compared to the patients without hypernatremia. Given the close relationship between sodium intake and natriuresis,[19] we hypothesize that sodium intake may explain natriuresis greater than 20 mmol/L, but not the observed hypernatremia.

The SARS-CoV-2 virus has a tropism for renal cells.[20] A study of 15 normal kidney samples analyzed the proportions of renal cells expressing both the host cellular
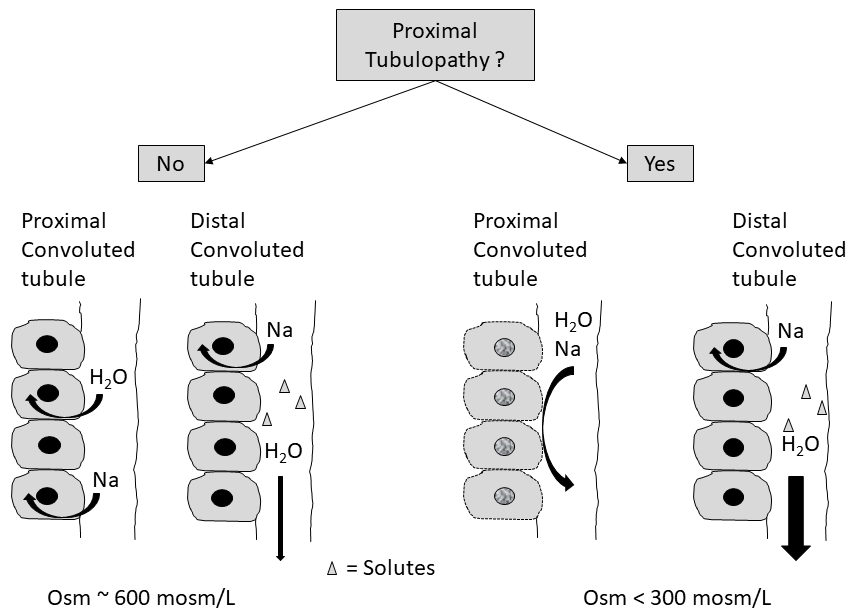
Figure 1: Tubulopathy of the proximal convoluted tubule and its impact on urine osmolality (OSM).

angiotensin converting enzyme II (ACE-2) receptor and the key transmembrane serine proteases (TMPRSS) family. ACE2 and TMPRSS genes were found to be jointly expressed by podocytes and proximal convoluted tubular cells, which are as a result the preferred targets of SARS-CoV-2, which can lead to renal failure.[21] Proximal straight tubular cells promote the reabsorption of 60% of excreted water. A tubulopathy (Figure 1) could have explained a loss of free water responsible for hypernatremia. Urinary osmolarity above 600 mOsm/L excluded this diagnostic possibility in our series.

CONCLUSION

Sodium is an important marker of hydration status more reliable than water balances, which do not measure insensitive losses and can mask silent hypovolemia. COVID-19 patients have significant insensible losses due to the presence of significant fever, anorexia with reduced fluid intake and the presence of diarrhea. Tubulopathy cannot explain the hypernatremia in our patients. Given the low proportion of septic shock and the prescription of fluid maintenance at the lower limit of the recommendations, we treated our patients in a very restrictive manner in terms of fluid administration with the consequence that 52% of patients experienced hypernatremia and renal failure. In ARDS without associated septic shock, the risk of silent hypovolemia should be kept in mind.

Limitations
This study is retrospective, monocentric, and the data was collected for only one day, which limits the number of patients studied. Daily monitoring of the weight of the patients, which would have aided in the assessment of the insensible losses of the patients, was not performed for technical reasons and the weight of the isolation protection measures. The advantage of the monocentric character of this study is its homogeneity of care.

Ethics approval and consent to participate
Our study received approbation of our medical committee (CE 2020/82). Given the retrospective nature of the study, we did not have to ask for a written informed consent.

Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests
The authors have no conflicts of interest to declare.

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