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Severe respiratory acidosis contributing to refractory hyperkalemia: a case series of COVID-19 patients with renal failure

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ABSTRACT

Introduction: Respiratory acidosis (RA) is not known to cause severe hyperkalemia. However, an exception to this general rule was observed in three patients with severe COVID-19 complicated with renal failure in our center.

Objectives: The current study investigated the explanation for hyperkalemia refractory to renal replacement therapy in patients with severe COVID-19 with hypercarbia and renal failure in a tertiary care center.

Patients and Methods: In this study, we present a case series of three patients with severe COVID-19 with hypercarbia and dialysis-requiring renal failure who developed persistent hyperkalemia refractory to renal replacement therapy. We studied various causes of persistent hyperkalemia, such as acid-base disorder, a high turnover state, exogenous administration, rhabdomyolysis, and hypoaldosteronism.

Results: All three patients initially presented with episodes of severe hyperkalemia, which were ameliorated after RA was corrected. All of these patients had worsening pulmonary function, after which the hyperkalemia could not be corrected, corresponding to persistent RA. The evidence that there was a contribution of RA to hyperkalemia was further strengthened by the observations of patient 1, in whom the hyperkalemia was only corrected after changing ventilator settings and who was unresponsive to dialysis. We studied the dialysate effluent in patient 3, and the results showed satisfactory removal of potassium with no improvement in the high serum potassium levels. Another interesting finding was that although the dialysate sodium concentration was greater than the serum sodium concentration, there was a decrease in the serum sodium concentration, indicating a reduced movement of sodium into the extracellular space.

Conclusion: In our study, metabolic acidosis alone could not explain the high serum potassium levels. Moreover, hyperkalemia was corrected after RA was corrected, indicating that the latter might have been the predominant cause of hyperkalemia in these scenarios. The presence of renal failure and low serum bicarbonate levels might have been the factors contributing to decreased Na+-K+-ATPase activity in the setting of RA, which contributed to severe hyperkalemia in all three patients.

Implication for health policy/practice/research/medical education:
Respiratory acidosis can be associated with refractory hyperkalemia in patients with renal failure. The absence of compensatory metabolic alkalosis and the presence of renal failure could be the explanation for this phenomenon. It might be difficult to treat hyperkalemia in such patients with renal replacement therapy without correcting respiratory acidosis.

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Case Series

Introduction

Acute kidney injury (AKI) and respiratory acidosis (RA) are common in patients with severe COVID-19 (1). In inorganic metabolic acidosis (MA), the serum potassium level changes with changes in the pH of the extracellular fluid (ECF). There have been conflicting results in studies on redistribution hyperkalemia due to acute RA. To the best of our knowledge, there have been no studies on

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whether RA can cause severe hyperkalemia (2-4). In inorganic metabolic acidosis, the pH changes more in the ECF than in the intracellular fluids (ICF). A decrease in the extracellular pH inhibits Na^+-H^+ antiporters, causing intracellular Na^+ depletion and reducing Na^+-K^+ ATPase activity. However, in RA, as CO_2 is freely permeable across the cell membrane, it lowers the pH in both the ECF and ICF to a similar extent, preventing a significant reduction in the function of the Na^+-H^+ antiporter and intracellular sodium depletion. In RA, ECF serum bicarbonate (HCO_3^-) increases due to compensatory metabolic alkalosis, leading to increased activity of the Na^+-$HCO3^-$ symporter, further preventing intracellular sodium depletion. A significant reduction in Na^+-K^+ATPase activity is not observed in RA due to intracellular sodium depletion, which can be explained by the above two factors (4). We report three cases of severe hyperkalemia refractory to renal replacement therapy (RRT) in COVID-19 patients with AKI and RA

Objectives

The current study investigated the explanation for hyperkalemia refractory to RRT in patients with severe COVID-19 complicated with hypercarbia in a tertiary care center.

Patients and Methods

Study design

In this study, we present a case series of three patients with severe COVID-19 hypercarbia with dialysis requiring renal failure who developed persistent hyperkalemia despite renal replacement therapy. Various reasons for persistent hyperkalemia, such as acid-base disorder, high turnover state, exogenous administration, rhabdomyolysis, and hypoaldosteronism, were investigated. Changes in serum potassium in relation to pH were studied, and whether the correction of hypercarbia with acidemia affected serum potassium was also explored. In patient 3 in the case series, we also measured potassium removal in the spent dialysate to better understand the possible explanation for refractory hyperkalemia.

Results

Patient 1

A 71-year-old male with severe COVID-19 with AKI was put on mechanical ventilation due to worsening hypoxia on Day 10. On the same day, he developed RA due to an endotracheal tube (ET) block. He was noted to have hyperkalemia, which was resolved by correcting his RA (Table 1). On Day 11, he developed worsening RA with refractory hyperkalemia. Hence, slow low-efficacy dialysis (SLED) was started. Hyperkalemia persisted despite 16 hours of SLED and improved after the inspiration/expiration ratio of the ventilator was changed. Hyperkalemia resolution was accompanied by a decrease in PCO2 and an increase in pH on day 12 (Table 1, Figure 1). On day 13, the RA became irreversible, and the hyperkalemia became refractory to SLED. The patient died on day 14.

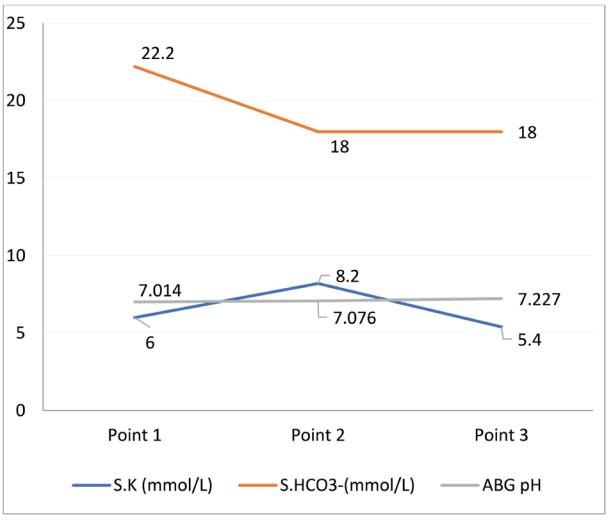

Figure 1. Serum potassium (SK^+) changes with changes in pH and serum bicarbonate ($S.HCO_3^-$) in patient 1. The above timelines applied during the administration of slow low-efficacy dialysis (SLED). Point 1: End of the 8th h of SLED; Point 2: End of the 9th h of SLED; Point 3: End of the 11th h of SLED (2 h after the change in ventilator setting to improve CO_2 washout).

Patient 2

A 63-year-old male with severe COVID-19 infection was put on mechanical ventilation due to worsening hypoxia on day 10. On Day 12, he developed RA and AKI. On day 13, the patient developed worsening RA (due to ET tube block) and hyperkalemia, which improved upon correcting his RA. On day 14, he developed refractory RA and refractory hyperkalemia (despite being on SLED), and he died on Day 15 (Table 1).

Patient 3

A 55-year-old male with severe COVID-19 developed AKI on day 19. He also presented with severe RA (due to ET tube block) and hyperkalemia, which improved upon correcting his RA. On day 20, he developed hyperkalemia refractory RA and was started on SLED. After 6 hours of SLED, his serum potassium level had only reduced by 0.8 mmol/L. However, it increased by 0.6 mmol/L in the next two hours with concomitant worsening RA (Figure 2). On day 21, he died due to refractory hypotension.

None of the patients received exogenous potassium or any drug causing hyperkalemia, and none had evidence of rhabdomyolysis. Serum aldosterone levels were elevated in all three patients, contrary to the expected reduction in hyperkalemia. There was no evidence of hypothyroidism in any of the above patients.

Discussion

Acute hyperkalemia is observed with exogenous potassium

Table 1. Biochemical analysis of three patients. Changes in the serum K^+ concentration in relation to blood pH, arterial blood gas pH (ABG-pH), serum creatinine (SCr), and serum potassium (SK^+), were detected in all three patients

Number of Days	pH	PCO_2 (mm Hg)	HCO_3^- (mmol/L)	SCr (mg/dl)	SK^+ (mmol/L)
Patient 1					
Day 10	7.472	23	17.6	2.3	3.8
Day 10	7.121	60.2	19.2	-	6.4
Day 10	7.4	26	19		4.6
Day 11	7.229	49.1	24.1	2.6	3.8
Day 11	6.964	103.8	23		8.2
Day 12	7.014	89.1	22.2		6
Day 12	7.076	62.9	18	5.2	8.2
Day 12	7.227	43	18		5.4
Day 13	7.033	84.4	21.9		7.5
Patient 2					
Day 13	7.334	40.4	21	1.4	4.9
Day 13	7.17	71.8	25.6	1.2	7.3
Day 13	7.34	44	24.6	-	5.2
Day 14	7.195	62.7	23.7		7
Day 14	6.996	93.7	20.9	3.0	7.7
Day 14	7.112	58.7	18.3		7.8
Patient 3					
Day 19	7.348	46.4	24.9	1.0	4.7
Day 19	7.203	63.7	24.5	1.6	6.7
Day 19	7.342	52	25	1.6	5.2
Day 20	7.25	48	22	2.8	6.1
Day 20	7.252	49.8	21.6		5.3
Day 20	7.131	62.7	20.4	3.5	5.9

administration or in cases of potassium redistribution (5). Redistribution hyperkalemia can be either due to increased cell permeability or the inhibition of Na^+-K^+ ATPase.

Acute regulation of Na^+-K^+ ATPase activity depends on the substrate concentration (intracellular Na^+, extracellular K^+, and ATP), kinetic properties or covalent modifications by hormones such as catecholamines, insulin, and thyroxine (6,7). The ICF pH, ECF pH, and ECF $HCO3^-$ concentration regulate the intracellular Na^+ concentration. A decrease in the ICF pH or an increase in the ECF pH stimulates the Na^+-H^+ antiporter, causing an increase in the intracellular Na^+ concentration (4). Other channels that regulate the intracellular Na^+ concentration are the Na^+-$HCO3^-$ symporter and Cl^- $HCO3^-$ antiporter, the activity of which depends on the ECF $HCO3^-$ concentration (4). Mineral acidosis causes redistribution hyperkalemia because only the ECF pH decreases during mineral acidosis. However, in RA, the ECF and ICF pH decrease with a concomitant increase in the ECF $HCO3^-$

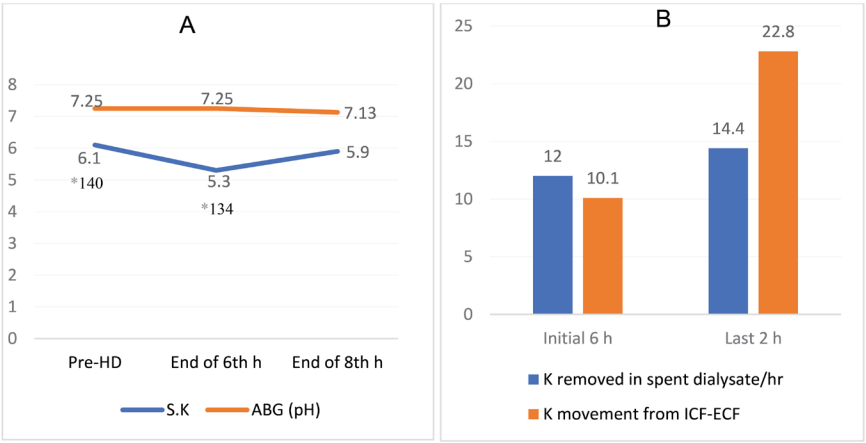

Figure 2. A. Changes in serum potassium (SK^+) and arterial blood gas (ABG) pH during slow low-efficacy dialysis (SLED) in patient 3. *Serum sodium (SNa^+) values were recorded before HD and at the end of the 6th hr of HD. **B**. Hourly removal of K^+ in the spent dialysate along the mentioned timeline and movement of K from the ICF to the ECF (hrly) was calculated as spent dialysate K^+ - {(change in $S.K^+$) × ECF volume}per hr, ECF volume calculated from 1/3 total body water (calculated from Watson's formula).

concentration (4). There are conflicting data on the role of RA in the redistribution of hyperkalemia, and to the best of our knowledge, there are no data on severe hyperkalemia due to RA (3-5).

In all the cases, the change in SK^+ per 0.1 pH decrease was greater than the expected value of 0.6 meq/L (8). There was no evidence of the exogenous administration of K^+ drugs causing redistribution hyperkalemia, rhabdomyolysis, aldosterone deficiency, or hypothyroidism in any of the described patients. ET tube blockade is more commonly observed in cases of severe COVID-19-related lung disease than in cases of other causes of acute respiratory distress syndrome, as seen here (8). Severe hyperkalemia was reversed after the correction of RA by the correction of the ET tube obstruction, which was observed in all the above patients. In patient 1, one instance of hyperkalemia refractory to renal replacement therapy improved after the correction of RA (Table 1). Although metabolic acidosis is known to cause redistribution hyperkalemia, it is less likely to be a significant contributor in any of these cases, as in none of the patients was the $S.HCO3^-$ value less than 17 mmol/L (9). All the above events indicate that RA was the predominant cause of hyperkalemia.

In patient 3, after the first six hours of SLED, his SK+ fell from 6.1 to 5.3 in the calculated ECF volume of 14 L (calculated based on the total body water calculation according to Watson's formula using the patient's weight at admission). The total K^+ removed during the first six hours of SLED was 72 meq (measured in dialysate effluent), but the decrease in K^+ in the total ECF was 11.2 meq (0.8 mmol/L × 14 L). Hence, 60.8 meq (84.4%) of K+ was removed from the ICF during the initial six hours after being redistributed to the ECF. In the last two hours, despite the removal of 28.8 mmol of K^+, his SK^+ increased by 0.6 mmol/L. Both situations showed significant K^+ movement from the ICF to the ECF. SNa^+ decreased from 140 to 134 in the initial six hrs of SLED with a DNa^+ of 140 mmol/L without any hypotonic fluid administration, suggesting the possibility of Na^+ movement from the ECF to the ICF. A significant K^+ shift from ICF to ECF despite a SK^+ level > 4 meq/L (the lowest SK^+ during HD-5.3 meq/L) and a concomitant reduction in SNa^+ suggest that the inhibition of Na^+-K^+ ATPase was probably due to RA (Figure 2) (9).

The hypercatabolic state in patients with COVID-19 can cause redistribution hyperkalemia due to high cell turnover (11). The contribution of a hypercatabolic state to hyperkalemia cannot be ruled out in the above three patients. However, if this was the predominant cause, their potassium levels would not have improved with the correction of RA, and there would not have been a simultaneous decrease in SNa^+, as in patient 3.

Usually, severe redistribution hyperkalemia is not observed in patients with RA because it does not significantly reduce Na^+-H^+ antiporter activity, and compensatory elevated ECF $HCO3^-$ (due to RA) increases the activity of the Na^+-$HCO3^-$ symporter, preventing intracellular Na^+ depletion (6).

In all the patients, the probable explanations for hyperkalemia due to RA were the absence of compensatory metabolic alkalosis and the presence of renal failure. A reduction in ECF $HCO3^-$ reduces Na^+-$HCO3^-$ symporter activity, causing a reduction in the intracellular Na^+ concentration and Na^+-K^+ ATPase activity and causing the redistribution of hyperkalemia, as was evident on 2 occasions. In patient 1 on day 12 during SLED, despite the increase in the pH from 7.014 to 7.076 with a concomitant decrease in HCO3- from 22.2 meq/L to 18.1 meq/L, his SK^+ increased from 6 meq/L to 8.2 meq/L (on H.D), and only after further correction of RA was the serum potassium reduced (Figure 1). In patient 2, on day 14, despite the increase in pH from 6.996 to 7.112 with a concomitant decrease in $HCO3^-$ from 20.9 meq/L to 18.3 meq/L, his SK^+ increased from 7.7 meq/L to 7.8 meq/L (on H.D.). On all occasions in which the correction of RA led to the correction of hyperkalemia, the change in the serum $HCO3^-$ concentration was < 1 mmol/L. In the situations mentioned above, in which an increase in pH due to the correction of RA did not correct the hyperkalemia, a decrease in the serum $HCO3^-$ > 2 mmol/L was noted. Renal failure associated with a reduction in K^+ excretion contributed to the increase in the severity of redistribution hyperkalemia.

Conclusion

Our study suggests the possibility that severe hyperkalemia can be due to RA in renal failure patients, probably due to low ECF HCO3- and reduced kidney function.

Limitations of the study

Data on potassium in the spent dialysate are available for only one patient, and intradialytic serum sodium changes are also available for only one patient. The above information might have provided additional clarity.

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Authors' contribution

Conceptualization: Nabadwip Pathak.
Data curation: Nabadwip Pathak.
Formal analysis: Nabadwip Pathak, Sunil Kumar Nanda
Investigation: Sunil Kumar Nanda.
Methodology: Nabadwip Pathak, Sunil Kumar Nanda.
Resources: Nabadwip Pathak.
Validation: Nabadwip Pathak.
Supervision: Sunil Kumar Nanda.
Visualization: Nabadwip Pathak.
Writing-original draft: Nabadwip Pathak.
Writing-review and editing: Sunil Kumar Nanda.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case series was conducted in accordance with the principles of the World Medical Declaration of Helsinki. The study was approved by the PIMS Institute ethics committee with IEC No. R.C./2020/78. The PIMS Institute ethics committee is registered with CDSCO-Reg.No.ECR/400/Inst/Py/2013. Informed consent was obtained from all patients' first-degree relatives. Furthermore, the authors have addressed all ethical issues, including plagiarism, data fabrication, and double publication.

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