



Hyperkalemia: do you forget something?

Matteo Landolfo¹ · Maria Valeria Di Rosa¹ · Luca Gasparotto¹ · Antonio Marchese¹ · Gianni Biolo¹

Received: 19 April 2022 / Accepted: 29 July 2022

© The Author(s), under exclusive licence to Società Italiana di Medicina Interna (SIMI) 2022

Case presentation

A fully SARS-CoV2 vaccinated man in his 80 s, with a previous history of surgically treated bladder and prostate cancer, was referred to the emergency department because of fever, diarrhoea cough and progressive dyspnea. At admission, haemodynamics was stable and arterial blood gases (ABG) showed a moderate type-1 respiratory failure pattern (paO₂ 55 mmHg, SATO₂ 88%, paCO₂ 25 mmHg). Laboratory findings were consistent with severe inflammation in mild leukopenia (WBC 2.500/μL) and no serum electrolyte imbalance. A resting standard 12-lead electrocardiogram (EKG) showed sinus rhythm and normal repolarization. Nasopharyngeal swab testing for the SARS-CoV2 genome with the RT-PCR method was positive. Chest computed tomography with contrast excluded pulmonary embolism and revealed progressive interstitial disease compatible with COVID-19 pneumonia and unilateral pleural effusion. Thus, the patient was addressed to our Internal Medicine Unit to continue adequate treatment and monitoring. According to the latest proposed treatment protocol for COVID-19, the patient was given oxygen by Venturi mask, intravenous corticosteroids, low-molecular-weight heparin (LMWH) and pump-proton inhibitor for thromboembolism and intestinal bleeding prevention, respectively. A low dose of loop diuretic was added to reduce the pleural effusion. Broad-spectrum antibiotics were also administered to cover possible associated bacterial infections. The diarrhoea stopped without further intervention. Even though renal function remained stable and no other treatment started, we observed progressive hyperkalemia (max 7.13 mEq/L) and typical ECG changes (Fig. 1).

Prof. Biolo: How frequent is hyperkalemia in hospitalized patients? Was the patient complaining of any symptoms?

Dr Di Rosa

Hyperkalemia, defined by serum potassium concentration exceeding 5.5 mEq/L, ranges from 2 to 10% in acutely hospitalized patients and is associated with increased mortality [1]. Hyperkalemia can progressively derange the physiologic cardiac electric activity, as elicited by the onset of typical ECG alterations: peaked T waves, prolonged PR interval, and wide QRS (Fig. 1) [2]. Severe cases can be life-threatening, leading to muscular paralysis, ventricular arrhythmias, and finally, asystole. Otherwise, most reported clinical manifestations of hyperkalemia may include neuromuscular and gastrointestinal symptoms such as muscle twitching and weakness, ascending paresthesia, and diffuse abdominal discomfort. If mild chronic hyperkalemia occurs, symptoms can be absent or subtle and nonspecific so that hyperkalemia is only discovered after routine laboratory tests. In particular, our patient did not complain of any potentially related symptoms.

Prof. Biolo: If the patient was asymptomatic, why did you ask electrolyte panel? Did you expect any electrolyte imbalance?

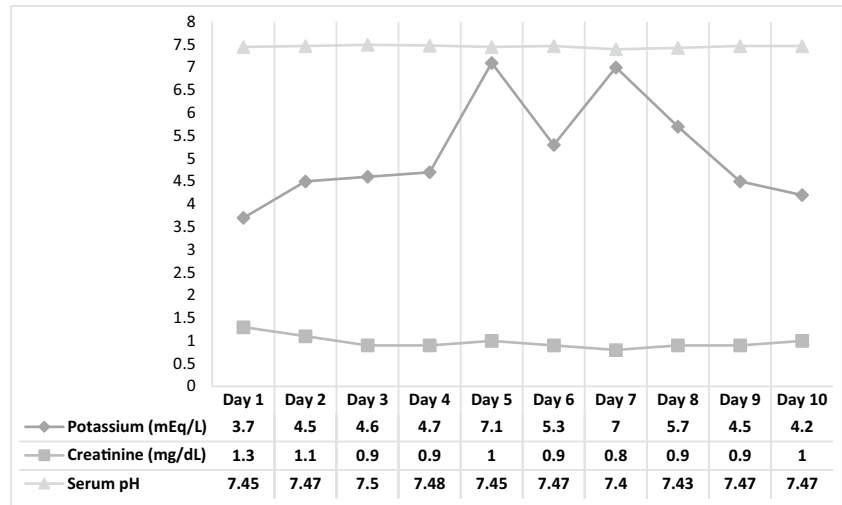
Dr Di Rosa

Initially, the patient had diarrhoea and was put under furosemide and high-dose corticosteroid treatment. We expected hypokalemia to occur due to gastrointestinal and renal losses, so we routinely monitored serum potassium concentrations.

✉ Matteo Landolfo
m.landolfo.doc@gmail.com

¹ Clinical Medicine, Department of Internal Medicine, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy

Fig. 1 Serum pH, creatinine and potassium trends during the hospitalization



Prof. Biolo: How the severe acute hyperkalemia was initially managed? Did you make any further diagnostic investigation?

Dr Gasparotto

According to the management protocol [3], serum potassium measurement was promptly repeated to rule out pseudohyperkalemia from wrong blood sampling or inadequate blood storage. After confirming hyperkalemia, intravenous calcium gluconate and dextrose 5% with insulin correction were beneficially administered. However, once treatment was suspended, serum potassium rose again. Patients with acute kidney injury or failure, hemolysis, and severe acidosis are more likely to develop acute hyperkalemia. Hyperkalemia is one of the most frequent complications in advanced chronic kidney disease (CKD), as the risk increases as the GFR progressively decreases. Still, hyperkalemia is generally considered once the glomerular filtration rate (GFR) becomes less than 15 mL/min because of the adaptive response in the remaining functional nephrons. On these bases, ABGs, serum creatinine and urea, hemolysis and rhabdomyolysis indices must be obtained first. Our patient had normal kidney function and remained hemodynamically unchanged throughout the hospitalization. ABGs and laboratory reported no acid–base disturbances, normal serum sodium and no findings related to blood or muscle cell rupture and leakage. An endocrine aetiology had to be excluded, so we looked for causes of hyperaldosteronism or acute adrenal failure [4, 5]. In our case, urinary low potassium output suggested renin–aldosterone axis imbalance, confirmed by elevated plasma renin activity (PRA) and aldosterone ratio. Any clinical or laboratory findings suggested acute adrenal failure (Table 1).

Prof. Biolo: What was your next move at this point?

Dr Marchese

Pharmacological therapies are the primary cause of hyperkalemia in up to 75% of hospitalized patients. Secondary to the renin–angiotensin–aldosterone system inhibition (RAASi), many drugs can interfere with potassium homeostasis by promoting transcellular shift or impairing renal excretion. Apart from ACE-inhibitors, angiotensin-receptor blockers, potassium-sparing diuretics (MRAs), azole anti-fungals, non-steroidal anti-inflammatory drugs (NSAIDs), and other molecules are related to hyperkalemia. In this context, the revision of the current pharmacological treatment, looking for potential side effects, exerts a pivotal role. We found that LMWH can cause iatrogenic hyperkalemia, even rarely [5]. Our patient was treated with potassium-wasting therapies such as loop diuretic and corticosteroids, and none of the mentioned drugs was administered. After enoxaparin was discontinued and replaced with fondaparinux, the serum potassium level promptly normalized, confirming our hypothesis.

Prof. Biolo: How can you explain this side effect from the pharmacological point of view?

Dr Landolfo

Heparin-induced hyperkalemia (HIH) might occur with unfractionated heparin (UH) and LMWH, even at prophylactic dosage. Heparin directly affects the zona glomerulosa of the adrenal glands, resulting in decreased number and

Table 1 First-level laboratory tests for common causes of hyperkalemia

Causes	Parameters	Mechanisms
Acute kidney injury or failure Chronic kidney failure	Creatinine/GFR Proteinuria Urinary output	Decreased blood perfusion Direct damage Glomerulopathies Bilateral obstruction of urinary tract
Hemolysis	Hemoglobin LDH Bilirubin Haptoglobin	Extrinsic: infections, tumors, auto-immune disorders Intrinsic: congenital
Rhabdomyolysis	CK Myoglobin Myoglobinuria	Extensive trauma, crush syndrome Malignant hyperthermia Iatrogenic Infections Autoimmune disorders
Acid–base disorders (metabolic or respiratory acidosis)	pH PaCO ₂ Bicarbonates Lactates	Cellular base–acid buffer
Adrenal failure/hypoaldosteronism	Serum sodium 24 h urine potassium Anti 21-OH ab PRA/aldosterone	Addison's disease Iatrogenic Corticosteroid withdrawal

GFR glomerular filtration rate, *LDH* lactic dehydrogenase, *CK* creatinine kinase, *PaCO₂* arterial partial pressure of carbon dioxide, *21-OH* 21-hydroxylase, *PRA* plasma renin activity

affinity of angiotensin-2 receptors and a subsequent decrease in aldosterone production. Decreased aldosterone, in turn, results in type 4 renal tubular acidosis with decreased renal potassium and hydrogen ion excretion in the distal convoluted tubule [6]. Excessive anticoagulation may also precipitate adrenal haemorrhage and acute insufficiency. A decrease in serum aldosterone and urinary levels after heparin administration was confirmed in some studies [7].

Prof. Biolo: What is the reported incidence of HIH? Are we concerned about raising heparin administration related to the COVID-19 pandemic?

Dr Landolfo

Approximately 7–8% of treated patients can develop HIH, and the onset is 1–3 days after exposure, generally resolving within 24 h of discontinuation [8]. Severe COVID-19 has been associated with an elevated risk of venous and pulmonary thromboembolism (VTE), even in anticoagulated patients [9]. Furthermore, as corroborated by autopsy findings, intravascular lung thrombosis has been proposed as one of the mechanisms sustaining respiratory failure in SARS-CoV2 pneumonia [10]. On these bases, guidelines and experts recommended pharmacological VTE prophylaxis strategies with LMWH in hospitalized patients with severe COVID-19 [11–13]. In this context, LMWH has been

preferred among all anticoagulants for its peculiar pharmacokinetics and pharmacodynamic properties. Short half-life, intravenous and subcutaneous formulation availability and fewer drug interactions reflect predictable anticoagulant responses, improving efficacy and safety [14]. In addition, LMWH seems to possess anti-inflammatory and immunomodulatory properties that can counteract lung damage progression [15]. Recent trials left no doubts about the protective role of early administration of LMWH in COVID-19 patients [16, 17]. The spreading of heparin administration in hospitalized patients (old, comorbid and with polypharmacy) because of the SARS-CoV2 pandemic should have been more than a reason for experts and societies to produce at least update or warnings. Surprisingly, international guidelines concerning hyperkalemia prevention, diagnosis and treatment [18] just mentioned heparin treatment among risk factors for hyperkalemia, without further indication about HIH management and prevention of recurrences.

Conclusions

Hyperkalemia is frequent in hospitalized patients, especially if they are older, comorbid and under multiple concomitant treatments. Clinical manifestations of hyperkalemia can range from asymptomatic to life-threatening. The accurate diagnostic approach and the appropriate management can be complex, requiring knowledge of the various underlying mechanisms sustaining hyperkalemia. A careful revision of

the pharmacological therapy is mandatory. Particular attention to HIH due to heparin TEV prevention and treatment during the COVID-19 pandemic should be paid, as we are elicited by presenting this case.

Declarations

Conflict of Interest Authors declare no conflict of interest.

Human and animal rights and Informed consent The patient provided informed consent for the use of his clinical data.

References

- Palaka E, Grandy S, Darlington O, McEwan P, van Doornewaard A (2020) Associations between serum potassium and adverse clinical outcomes: a systematic literature review. *Int J Clin Pract* 74(1):e13421
- Montague BT, Ouellette JR, Buller GK (2008) Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol* 3(2):324–330
- Rafique Z, Peacock F, Armstead T, Bischof JJ, Hudson J, Weir MR et al (2021) Hyperkalemia management in the emergency department: an expert panel consensus. *J Am Coll Emerg Physicians Open* 2(5):e12572
- Hunter RW, Bailey MA (2019) Hyperkalemia: pathophysiology, risk factors and consequences. *Nephrol Dial Transplant* 34(Suppl 3):iii2–iii11
- Eleftheriadis T, Leivaditis K, Antoniadis G, Liakopoulos V (2012) Differential diagnosis of hyperkalemia: an update to a complex problem. *Hippokratia* 16(4):294–302
- Oster JR, Singer I, Fishman LM (1995) Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 98(6):575–586
- Sherman RA, Ruddy MC (1986) Suppression of aldosterone production by low-dose heparin. *Am J Nephrol* 6(3):165–168
- Koren-Michowitz M, Avni B, Michowitz Y, Moravski G, Efrati S, Golik A (2004) Early onset of hyperkalemia in patients treated with low molecular weight heparin: a prospective study. *Pharmacoevidemiol Drug Saf* 13(5):299–302
- Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M et al (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 18(7):1743–1746
- Levi M, Thachil J, Iba T, Levy JH (2020) Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 7(6):e438–e440
- Marietta M, Ageno W, Artoni A, De Candia E, Gresele P, Marchetti M et al (2020) COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISST). *Blood Transfus* 18(3):167–169
- Cuker A, Tseng EK, Nieuwlaar R, Angchaisuksiri P, Blair C, Dane K et al (2021) American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv* 5(3):872–888
- Gerotziakas GT, Catalano M, Colgan MP, Pecsvarady Z, Wautrecht JC, Fazeli B et al (2020) Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. *Thromb Haemost* 120(12):1597–1628
- Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R et al (2001) Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 119(1 Suppl):64s–94s
- Zufferey PJ, Dupont A, Lanoiselee J, Bateurs A, Poissy J, Goutay J et al (2021) Pharmacokinetics of enoxaparin in COVID-19 critically ill patients. *Thromb Res* 205:120–127
- Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanjoo S et al (2021) Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med* 181:1612
- Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN et al (2021) Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med* 385(9):777–789
- Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ et al (2020) Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 97(1):42–61

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.