The Management of Co-Morbidities in Patients with Heart Failure – Potassium Balance

Ewa A Jankowska

1. Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland. 
2. Cardiology Department, Centre for Heart Diseases, Military Hospital, Wroclaw, Poland

Corresponding author:
Cardiology Department, Centre for Heart Diseases, Military Hospital, Wroclaw, Poland
Email: ewa.jankowska@umed.wroc.pl

Abstract

Both hypokalaemia and hyperkalaemia are common in HF patients. They are each associated both with HF and with the many drugs used for HF. They are important as they both can aggravate ventricular arrhythmias, both can cause symptoms in HF patients and in the case of hyperkalaemia in particular, are a common reason not to prescribe or reduce the dose of or even cease use of effective medication with life- prolonging benefits in HFrEF, including ACEI’s and MRA’s. Treatment options for both hypokalaemia and hyperkalaemia are discussed including the emerging evidence that agents such as patiromer may be safe and effective agents to be used long-term in high-risk patients with HF to allow them to take doses of RAAS inhibitors in particular which they otherwise may not be able to take. This might allow them to continue to receive the mortality morbidity benefits these treatments confer.

Background

Both hypokalaemia and hyperkalaemia are common in HF patients. They are each associated both with HF and with the many drugs used for HF. They are important as they both can aggravate ventricular arrhythmias, both can cause symptoms in HF patients and in the case of hyperkalaemia in particular, are a common reason not to prescribe or reduce the dose of or even cease use of effective medication with life-prolonging benefits in HFrEF, including ACEI’s and MRA’s.

Potassium control

90% of the body’s stores of potassium (K⁺) are held intracellularly. What is measured in plasma represents less than 1% of total body K⁺. Serum potassium is normally regulated within a narrow range of 3.5 to 5.0 mmol/L, despite large variation in intake through food and drinks. Homeostasis is maintained both by control of the renal excretion and loss from the gut, and by regulating movements of K⁺ between intracellular and extracellular compartments. Excretion in HF is abnormal because of the use of diuretics (loop and thiazides increase excretion) and because of impaired renal blood flow and GFR. Aldosterone elevation increases potassium loss and internal shifts of K⁺ are under the influence of insulin and catecholamines, both of which mechanisms are altered in HF. Lastly ACEI’s, ARB’s and MRA’s all increase K⁺ levels in the serum.

Renal K⁺ excretion is mediated by aldosterone and by GFR. K⁺ is filtered by the glomerulus, and partially reabsorbed in the proximal tubule, paralleling sodium and water exchange. This absorption in the proximal part of the nephron passively follows that of Na⁺ and water, whereas reabsorption in the thick ascending limb of the loop of Henle is mediated by a Na⁺/K⁺/Cl⁻ carrier (NKCC2). K⁺ is later secreted by the connecting segment, the cortical and outer medullary collecting tubule, and the collecting duct via luminal potassium channels, and the activity of this secretion largely determines the degree of urinary K⁺ loss through the kidney, although reabsorption through the intercalated cells in the cortical and outer medullary collecting tubules via an active ATPase pump can affect K⁺ loss.

Hypokalaemia

Hypokalaemia when usually defined as a serum potassium concentration below 3.5 mmol/L is found in about 20% of hospitalized patients, most frequently in HF and multi-organ failure patients. Hypokalaemia can result from alterations in both long term (largely renal) or short term (transcellular shifts) or by excessive potassium losses from the gut, such as in severe diarrhoea. Transcellular shifts can occur in response to a surge in catecholamines or by acid-base disturbances. Loop or thiazide diuretic use and hyper-aldosteronism both worsen renal potassium losses in CHF.
Hypokalaemia is frequently detected only by routine blood testing. Symptoms to make one suspicious may include muscle weakness, constipation, or worsening oedema or higher grade arrhythmias. In CHF, even mild hypokalaemia may worsen ventricular arrhythmias. Severe hypokalaemia can rarely cause myopathy and paralysis with the risk of respiratory arrest at levels <2.0 mmol/L. The treatment of mild hypokalaemia detected routinely can involve recommending high potassium foods or prescribing potassium supplements, although these should be reviewed regularly because of the risk of hyperkalaemia in these patients. Intravenous potassium administration is rarely indicated because of the risk of overshoot hyperkalaemia, except for very difficult to control arrhythmias in which case continuous monitoring, with no more than 20 mmol/hr K+ administered, and regular reassessment of the serum potassium level after every 60 mmol is given. Concomitant hypomagnesaemia may need to be corrected at the same time effective to correct the hypokalaemia fully.

Hyperkalaemia

Hyperkalaemia is defined as a serum potassium concentration higher than 5.0 mmol/L. Pseudohyperkalaemia can occur with haemolysis, so repeat testing taking blood without a tourniquet and heparin can also impair the excretion of K+.

Hyperkalaemia occurs in 1% to 10% of all hospitalized patients with a noticeable increase in HF,[2,3] after the widespread uptake of MRA's for HF after the results of the RALES study. Most hyperkalaemia is caused by impaired potassium excretion from renal insufficiency. Drugs such ACEI's, ARB’s MRA’s and potassium-sparing diuretics (e.g., spironolactone, triamterene, sometimes used as adjunct diuretics in resistant oedema, or to assist in preventing hypokalaemia) will increase the risk of hyperkalaemia. Nonsteroidal anti-inflammatory drugs (NSAIDs) to assist in preventing hypokalaemia) will increase the risk of sometimes used as adjunct diuretics in resistant oedema, or to assist in preventing hypokalaemia) will increase the risk of hyperkalaemia. Nonsteroidal anti-inflammatory drugs (NSAIDs) and heparin can also impair the excretion of K+.

Hyperkalaemia is frequently detected by routine blood testing. Symptoms and signs to make one suspicious include muscle weakness, cardiac conduction disturbances, “tented” T waves, QRS widening, and bradycardia, however these ECG changes are not closely related to the level of serum potassium. The toxic effects of hyperkalaemia can be enhanced by hypocalcaemia, hyponatraemia and acidosis.[4] Severe severe acute hyperkalaemia (>6 mol/l) can lead to cardiac arrest and death,[5] with a mortality rates of up to 30% in severe uncorrected hyperkalaemia.[6]

The management of severe acute hyperkalaemia (>6 mol/l) may require short-term cessation of potassium retaining agents and inhibitors of the RAAS, but this should be minimized and RAAS inhibitors should be carefully reintroduced as soon as possible whilst monitoring potassium levels. Other emergency treatments include intravenous insulin and glucose, nebulized or inhaled beta-2–receptor agonists and calcium gluconate salts. Haemodialysis may be required in severe prolonged hyperkalaemia. A Cochrane review found no trial evidence of major outcome benefit for any emergency hyperkalaemia therapy with the best efficacy when medical (as opposed to dialysis) potassium lowering is required was for beta agonists and intravenous insulin-and-glucose.[7] The safety of neither therapy has been established specifically in the HF population. In view of their risks beta agonists are usually avoided in HF.

For chronic management of the risk of hyperkalaemia gut-active potassium binding agents have been shown to lower serum potassium including in HF patients and trial evidence to assessed their long term safety and benefit in HF would be valuable. For patients at risk of serious hyperkalaemia chronically, sodium polystyrene sulfonate (an ion-exchange resin that binds potassium in the colon) has been used but it frequently causes gastrointestinal disturbance as well as increasing the risk of sodium loading, hypomagnesaemia, hypocalcaemia, and colonic necrosis.

One frequently under-recognised risk of high potassium levels (even if only intermittent) is that evidence-based, life-saving medications may be under-dosed or stopped altogether. This could put patients at increased risk and could in the end be an increased burden to health care costs due to increased re-hospitalisation rates for HF. Therefore there is an important unmet need for novel therapeutic options for the long-term management of patients with, and at risk for, hyperkalaemia. Newer potassium binders for the treatment of hyperkalaemia have recently been approved.[8] Patiromer is a cation exchange polymer that exchanges calcium for potassium in the GI tract. It decreases serum potassium, and protects against episodes of recurrent hyperkalaemia. In the OPAL-HK trial this has been shown to reduce the need discontinuation of RAAS inhibitors[9] an outcome likely to be of significant clinical benefit in HF patients. In this trial in CKD patients (42% also with heart failure) with baseline potassium levels of 5.1–6.5 mmol/l treated initially with open label patiromer were then randomised to double blind continuation of patiromer or withdrawal (control) over 8 weeks. A recurrence of hyperkalaemia (potassium level, ≥5.5 mmol/l) occurred in only 15% of patiromer treated patients compared to 60% in control patients up to 8 weeks (p<0.001). All the patients were receiving at least one RAAS inhibitor at baseline and at the end of the randomized withdrawal phase, 44% in the placebo group as compared with 94% in the patiromer group were still receiving RAAS inhibitors. If this difference could be maintained long term there may well be significant survival benefits of using this agent long term HF patients at high risk of hyperkalaemia if indeed effective doses of ACEI’s and MRA’s can be maintained significantly more frequently by such a strategy.

In a pre-specified analysis of HF patients in OPAL-HK 142 patients (42% of the overall trial) the change in serum K+ from baseline to week 4 was −1.06 ± 0.05 mEq/L and 76% of patients achieved serum K+ levels of 3.8 mEq/L to <5.1 mEq/L. In the randomized withdrawal phase, the median increase in serum K+ from baseline of that phase was greater with placebo (n = 22) than patiromer (n = 27) (P < 0.001) and recurrent hyperkalaemia (serum K+, ≥5.5 mEq/L) occurred in 52% on placebo and 8% on patiromer (P < 0.001), confirm similar efficacy and safety in HF patients.

Two other trials (PEARL-HF and AMETHYST-DN) examined the safety and efficacy of patiromer in patients with hyperkalaemia or at risk for hyperkalaemia and receiving RAAS inhibitors. The PEARL-HF study increased the proportion of patients able to titrate their spironolactone dose from 25 mg/day to 50 mg/day in patients with a history of hyperkalaemia or an eGFR of <60 mL/ min. The AMETHYST-DN study demonstrated that patiromer maintained mean serum potassium ≤5.0 mEq/L for up to 1 year with a low rate of hypokalaemia.[10] The increasing evidence

DOI: 10.17987/icfj.v10i0.457
suggest agents such as patiromer may be safe and effective agents to be used long-term in high-risk patients with HF to allow them to take doses of RAAS inhibitors in particular which they otherwise may not be able to take. This would allow them to continue to receive the mortality morbidity benefits these treatments confer.

Declaration of Interest
The author has no conflicts of interest to disclose.

Acknowledgements
The author has abided by requirements for ethical publishing in biomedical journals [11].

References