Potassium levels in acute myocardial infarction: definitely worth paying attention to

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This editorial refers to ‘Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction’ by M.L. Krogager et al., on page 245.

Congestive heart failure (CHF) is a common comorbidity following acute myocardial infarction (AMI), and CHF complicating AMI has an unfavourable outcome. Water and sodium retention are the key pathophysiological events leading to ‘congestion’ in CHF. It is now clear that CHF is the result of a systemic neurohormonal response involving the heart, kidneys, and vasculature.

Neurohormonal response in congestive heart failure

Two main neurohormonal systems play a central role in CHF: the renin–angiotensin–aldosterone system and the adrenergic autonomic nervous system (Figure 1).¹ Myocardial injury, impaired diastolic and systolic function, peripheral hypoperfusion, and pulmonary venous hypertension collectively activate the neurohormonal response, which primarily exists to maintain homeostasis that we now know participates in further injury.

Imagine a ‘cave man’, a hunter, who survives on his prey, and competes with other animals for it. The most likely adverse event is to be assaulted and wounded leading to blood loss. The neurohormonal response would immediately be triggered. Norepinephrine release from the nerve endings would increase heart rate, cardiac contractility, and therefore cardiac output. To compensate for the blood loss, norepinephrine would shift the blood flow way from non-vital organs (i.e. skin, gut) to the vital organs (i.e. brain, heart, lungs), and also decrease flow to the kidney to reduce filtration, promote re-absorption, and therefore, reduce volume loss with urine. Hypoperfusion and renal vasoconstriction would activate renin in the kidney, leading to maturation of angiotensin II. Angiotensin II acts as a powerful vasoconstrictor, potentiating the effects of norepinephrine, increasing vascular resistance in non-vital organs, and further reducing renal filtration. Aldosterone, produced in the adrenal glands in response to Angiotensin II, is a powerful anti-natriuretic hormone, inducing sodium reabsorption in exchange for potassium in the renal tubules and the gut, leading to increase sodium and water content in the body. Despite the blood loss resulting from the struggle, the ‘cave man’ manages to survive, catch the prey, seek shelter, reinstitute his fluid balance by drinking water and his iron deficit by eating meat, ultimately restoring homeostasis.

Congestive heart failure after AMI is a very different scenario. The systemic hypoperfusion seen in AMI is not a result of net volume loss but rather impaired cardiac diastolic or systolic function. Norepinephrine increases heart rate and cardiac contractility leading to an initial sustainment of cardiac output, but also an expansion of the ischaemic injury in AMI that favours arrhythmogenesis. The vasoconstriction induced by norepinephrine and angiotensin may be helpful in the immediate response to maintain cerebral perfusion, but soon becomes detrimental as it opposes an increased resistance to cardiac output, thus further enhancing CHF. Reduced renal perfusion and increased sodium/water reabsorption lead to hypervolemia, which is not reduced in CHF, and favours more ‘congestion’, enhances pulmonary venous hypertension, and leads to higher systemic venous pressure which ultimately further opposes renal filtration.

What does potassium have to do with all this?

Serum potassium levels are tightly controlled in humans between 3.5 and 5.0 mmol/L through sophisticated controls at the organism, cellular, and molecular level. Derangements in the neurohormonal response in CHF are reflected in the serum potassium levels and the body’s attempt to maintain a normal value.

Renal hypoperfusion and pre-glomerular vasoconstriction leads to reduced glomerular filtration promoting potassium retention and hyperkalaemia (Figure 1). Aldosterone release, however, promotes a re-absorption of sodium in exchange of potassium favouring hypokalaemia (Figure 1). Norepinephrine induces an intracellular shift of potassium, also promoting hypokalaemia. Congestive heart failure often requires diuretics to manage symptoms of congestion.
Loop diuretics are the most potent diuretics and are commonly prescribed to relieve congestion related to CHF. Hypokalaemia is common because these agents reduce potassium reabsorption through the Na–K–2Cl symporter. Angiotensin and aldosterone blockers are often prescribed in patients with, or at risk for, CHF and counteract the hypokalaemic effects of neurohormonal activation, thus promoting hyperkalaemia. A significant reduction in renal blood flow due to reduced cardiac output increase in systemic venous pressure, neurohormonal-induced vasoconstriction, or an excessive use of diuretics leading to hypovolemia can all lead to severe renal hypoperfusion and acute kidney injury with associated risk of hyperkalaemia.

Considering all these factors, one wonders how does the potassium level remain stable in the complex scenario of CHF in its treatment? Well it does not.

### Prognostic role of potassium levels in congestive heart failure and acute myocardial infarction

Krogager et al.\(^2\) used Danish health registries to investigate the relationship between seven defined potassium intervals and 90-day all-cause mortality in patients following an AMI. The authors based the survival analysis on the first measured potassium, while excluding day 0 and 1 to minimize bias. Unsurprisingly, potassium levels outside the normal range were associated with increased mortality risk, with a characteristic U-shaped curve. This is not a novel finding in AMI.\(^3\)–\(^5\) The finding of the multivariable analysis in this report, however, reinforces the association between potassium levels well within the normal range of 3.5–3.8 mmol/L (HR: 1.84; 95% CI: 1.23–2.76) and 4.5–5.0 mmol/L (HR: 1.55; 95% CI: 1.09–2.21) and increased risk of mortality when compared with 3.9–4.5 mmol/L.

### Should we attempt to maintain potassium levels between 3.9 and 4.5 mmol/L?

Krogager et al.\(^2\) concluded that closer monitoring of potassium in patients with acute heart failure might improve survival. While this is possible, it is still unproven.

Fluctuations in potassium levels are common in patients with AMI and CHF; therefore, is a single potassium level the best predictor for mortality? Although potassium predicts mortality, does it cause death per se? The report by Krogager et al.\(^2\) lacks details regarding the cause of death, and while changes in potassium are pro-arrhythmic, one would want to see a specific association with arrhythmic death. It is indeed possible that potassium levels are a marker for worse disease rather a mechanism of disease. Therefore, would aggressive monitoring and correction of potassium levels improve mortality? Possibly, if one could prevent the arrhythmic deaths related to markedly abnormal potassium. But how frequent should the monitoring be? How would one go about ‘fixing’ potassium levels? Would there be a risk for overcorrection? Could some medications still be beneficial even if they mildly increase potassium levels (i.e. angiotensin/aldosterone blockers)? And will all treatments equally impact potassium levels and mortality?

### Conclusions

Congestive heart failure complicating AMI is a high-risk condition associated with high mortality. Changes in potassium levels, even if mild and within the normal range, predicted worse outcomes in this cohort. Whether potassium levels should be monitored, or how frequently, and whether any treatment is warranted for mild changes remains unknown.

### References