Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 1

Can we treat heart failure effectively and maintain potassium homeostasis? A clinician's perspective

IAIN SQUIRE

Abstract

Hypokalaemia and hyperkalaemia are common complications of heart failure and its treatment: either may increase markedly the risk of arrhythmias and sudden cardiac death. Hypokalaemia predominates in the early stages of heart failure. The risk of hyperkalaemia increases as renal function declines, usually in the context of advancing heart failure. For patients with heart failure, serum potassium levels of between 4.5–5.5 mmol/L are recommended. Monitoring of serum potassium is essential, with more frequent monitoring in patients with moderate renal failure, relatively high serum potassium, or in those at high risk of renal impairment, e.g. elderly or diabetic patients. Hypokalaemia can be ameliorated by a potassium-sparing diuretic or an aldosterone receptor antagonist; increasing dietary potassium intake or taking potassium supplements is less effective. Doses of loop or thiazide diuretics should be optimised. Hyperkalaemia is more often seen in advanced heart failure. Restriction of dietary potassium and withdrawal of potassium supplements are standard. Temporary discontinuation of angiotensin-converting enzyme inhibitor and/or aldosterone receptor antagonist therapy may be appropriate but attempts should be made to reintroduce these. Excessive diuretic therapy should be avoided. With routine potassium monitoring and pre-emptive intervention included in heart failure protocols, the risks to patients can be minimised.

Key words: potassium, hyperkalaemia, hypokalaemia, heart failure, congestive heart failure, ACE inhibition, aldosterone.

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Introduction

Electrolyte disturbances are common in chronic heart failure (CHF) and are more likely to provoke adverse clinical consequences than in healthy individuals due to the abnormal cardiovascular conditions that characterise CHF.[1] Disturbances to sodium, potassium and magnesium balance are common, often occurring together, and are interrelated to one another. Loss of potassium homeostasis encompasses two competing dangers: hypokalaemia and hyperkalaemia. Even in the situation of normal electrolyte balance, patients with CHF are vulnerable to arrhythmias and indeed sudden cardiac death accounts for up to half of all mortality in CHF.[2] Myocardial ischaemia, patchy fibrosis and pro-arrhythmic sympathetic activation may all play a role, and inadequate or excess levels of potassium are important contributors to electrical instability in the myocardium.[3] Both conditions have potentially life-threatening consequences by increasing the risk of arrhythmias and sudden cardiac death.[1,4-7] Accordingly, monitoring for potassium imbalance, the identification of individuals at higher risk and preventive intervention should be integral to CHF management strategies.

CHF predisposes to potassium imbalance through a variety of mechanisms (table 1). Activation of the renin-angiotensin-aldosterone system (RAAS) exerts a powerful influence on potassium regulation,[1,5] while deteriorating renal function, related to CHF disease progression and/or concomitant conditions, contributes by restricting the kidneys' ability to regulate potassium excretion

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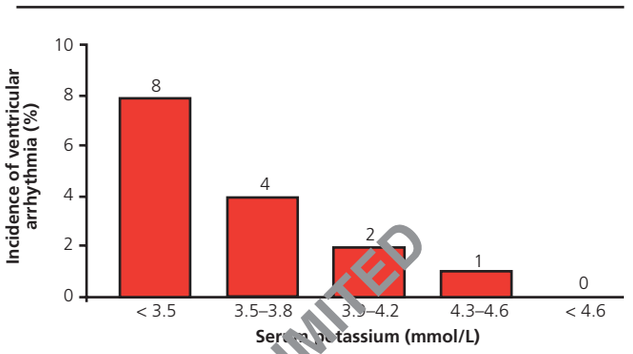
Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 2

Table 1. Disease-related and drug-related factors contributing to risk of potassium imbalance in heart failure

Factors contributing to risk of hypokalaemia	Factors contributing to risk of hyperkalaemia
RAAS activation	Renal insufficiency
Diuretic therapy	Potassium supplements
Volume overload	Potassium-rich diet
Systemic alkalosis	Conditions which reduce potassium entry to cells e.g.: - diabetes with insulin deficiency - beta blocker dose increase - progressive metabolic acidosis
Inadequate potassium intake	ACE inhibitors Angiotensin II receptor antagonists Aldosterone receptor antagonists

Key: RAAS = renin-angiotensin-aldosterone system; ACE = angiotensin-converting enzyme

Figure 1. Relationship between serum potassium concentration and incidence of ventricular fibrillation among 537 patients upon admission to hospital for acute myocardial infarction



Adapted from Hulting J[20]

effectively. Superimposed on these intrinsic abnormalities, however, are the effects of CHF medications, notably angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs),[8-11] and aldosterone receptor antagonists.[12-14] These reduce aldosterone activity levels to varying degrees, thus influencing one of the primary endocrine functions of aldosterone, namely regulation of potassium excretion through the distal renal tubules. These agents therefore tend to increase the risk of hyperkalaemia. Beta antagonism exerts a relatively modest hypokalaemic effect.[15] Diuretics, other than those that are specifically potassium-sparing, are potent kaliuretic agents[4,16,17] partly as a result of stimulating the RAAS system.[18] Typically, hypokalaemia tends to occur more frequently in the early stages of CHF before development of significant renal dysfunction. As renal function declines and potassium excretion becomes increasingly impaired, the risk of hyperkalaemia increases.[6]

This article focuses on the effect that the major CHF drug classes can exert on potassium homeostasis, and considers the implications for monitoring and modification of pharmacological intervention.

Hypokalaemia in heart failure

It is difficult to obtain an accurate estimate of the incidence of hypokalaemia in CHF; the definition of hypokalaemia varies, as do the triggers to therapeutic intervention. Moreover, hypokalaemia is not routinely reported in the literature, particularly as regards the incidence in standard CHF populations. In one major trial (a population of patients with heart failure soon after acute MI, and for the most part receiving an ACE inhibitor in combination with beta blocker and diuretic therapy), serious hypokalaemia (serum potassium < 3.5 mmol/L) was reported in 13% of patients over a 16-month period.[13] This was twice as frequent as serious hyperkalaemia.

Hypokalaemia has a multifactorial aetiology in CHF. Elevated plasma aldosterone levels act on the renal tubule, enhancing sodium retention at the expense of increased potassium excretion. Volume overload may contribute by diluting the available potassium, while systemic alkalosis promotes cellular potassium uptake with consequent falls in serum potassium concentration. Diuretics increase sodium delivery to distal nephrons, stimulating potassium excretion, and also contribute to activation of the RAAS with an associated increase in aldosterone activity. Beta agonists, particularly those which act on the beta-2 receptor, can also play a part by stimulating movement of potassium into tissues.[15]

Whatever the balance of causal factors in an individual patient, hypokalaemia is a strong independent predictor of mortality in CHF.[19] Declining serum potassium levels confer a markedly increased risk of ventricular arrhythmias (figure 1);[20] the Multiple Risk Factor Intervention Trial (MRFIT) reported a 28% increase in risk of ventricular arrhythmia for every 1 mmol/L fall in serum potassium level.[21] This, in turn, increases the likelihood of sudden cardiac death,[7,22,23] a risk that is exacerbated in the setting of CHF.[1]

Hyperkalaemia in heart failure

The development of hyperkalaemia in CHF is much less common than hypokalaemia. As CHF progresses and cardiac output falls, renal perfusion is reduced; progressive renal dysfunction develops in parallel with increasing severity of CHF. The pharmacological effects of ACE inhibitors, ARBs and aldosterone receptor antagonists, all of which inhibit potassium excretion via a fall in aldosterone activity, increase the likelihood of hyperkalaemia. These effects are compounded by failing renal function and a growing inability to regulate potassium and sodium exchange effectively. Thus the disease itself, and its pharmacological therapy, tends to be seen more frequently in patients with more severe disease.[6] Patients with impairment of renal function, most often manifesting as raised serum creatinine, are thus at increased risk of hyperkalaemia.[13] There is also an increased propensity to hyperkalaemia in patients with diabetes,[6] partly due to diabetes-

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Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 3

Table 2. Relative risk of arrhythmic death in 6,797 patients with left ventricular dysfunction according to type of diuretic therapy (multivariate analysis)[27]

Type of diuretic	Relative risk	P value
No diuretic	1.00	Reference value
Any diuretic	1.37	0.009
Non-potassium-sparing	1.33	0.02
Potassium-sparing[a]	0.90	0.6

Key: [a]Either alone or in combination with a non-potassium-sparing diuretic

related abnormalities in RAAS functioning as well as onset of diabetic nephropathy. Patients with a high dietary or supplementary potassium intake are more vulnerable to the kidneys' declining capacity to excrete potassium. As with hypokalaemia, hyperkalaemia can be potentially life-threatening, by predisposing to cardiac arrhythmias with associated risk of sudden cardiac death.[4,6]

Pharmacotherapy and potassium homeostasis in CHF

Diuretics

Diuretics represent the most effective therapeutic option for symptomatic relief of CHF symptoms.[18] While generally associated with a relatively favourable safety profile, diuretic therapy has been linked to increased risk of ventricular arrhythmias and sudden cardiac death.[4,24] Although, as a class, diuretics stimulate renin release with consequent rises in angiotensin II and aldosterone,[18,25,26] there are significant differences in the propensity of different diuretics to induce hypokalaemia. Meta-analysis suggests differences in the rates of sudden (by implication arrhythmic) death in CHF (table 2),[27] suggesting differences in the association of diuretic classes with arrhythmias. In this context, direct comparisons of different diuretics in CHF are rare. A direct, causal effect of electrolyte disturbance and malignant arrhythmias in CHF has not been established prospectively. We must bear in mind that the severity of disease, and other factors, is likely to impact upon the choice and dose of diuretic. Similarly, factors other than the diuretic will contribute to the propensity of any individual patient to cardiac arrhythmias.

Thiazides result in a greater reduction in serum potassium than either loop diuretics or acetazolamine, while spironolactone, amiloride and triamterene are considered to be 'potassium-sparing'.[17] Patients prescribed potent loop diuretics, the most common type of diuretics used in CHF, are in general co-prescribed ACE inhibitor or ARB therapy, helping to counter potassium loss.[18] Where hypokalaemia occurs, a number of alternative courses of action may be considered, depending upon clinical examination and other biochemical findings. Reduction in the dose of loop diuretic may be appropriate. Alternatively, careful addition of a potassium-sparing diuretic may be indicated.

As the severity of CHF progresses, renal function declines and renal potassium excretion declines correspondingly. In those patients with renal insufficiency who are taking potassium-sparing therapy (ACE inhibitor, ARB, potassium-sparing diuretic, or potassium supplement) in conjunction with potent diuretics, the risk of hypokalaemia declines and the likelihood of hyperkalaemia increases correspondingly. Diuretic-related hyperkalaemia is rarely seen in the absence of significant renal dysfunction.

ACE inhibition and angiotensin II receptor blockade

The clinical benefits of ACE inhibition and ARB therapy in CHF are well established,[28-34] and these form the mainstay of CHF therapy. Part of this benefit may be due to maintenance of physiological electrolyte levels and prevention of ventricular arrhythmias.[29,32] Potentially, however, this retention of potassium can be detrimental. Both ACE inhibitors and ARBs affect renal elimination of potassium,[11,35] and can cause chronic hyperkalaemia by a variety of mechanisms including reductions in glomerular filtration rate (GFR) or aldosterone excretion.[5,11,36] Acute renal insufficiency associated with ACE inhibitors is usually reversible,[36] but heightens the risk of ventricular irregularities and sudden death.

It is important to be aware that hyperkalaemia can also manifest abruptly in patients receiving long-term ACE inhibitor or ARB therapy, with or without an associated fall in GFR, for example, if diarrhoea develops. However, ACE inhibitors/ARBs seldom cause clinically significant hyperkalaemia in the absence of renal dysfunction;[3] indeed, in patients with preserved renal function, administration of an ACE inhibitor often results in no change or even a rise in GFR due to improved renal blood flow. Where renovascular disease exists, GFR may be intimately linked to angiotensin II levels. In such circumstances ACE inhibitors/ARBs should be used with caution or renal impairment with sudden hyperkalaemia may result. Further to this, the occurrence of significant renal impairment in response to initiation of ACE inhibitor or ARB therapy should alert the physician to the possibility of renovascular disease.

Early evidence suggested that ARBs may have a slightly lesser effect on potassium excretion than ACE inhibitors,[35,38] possibly because they do not accumulate significantly in the presence of renal failure.[39] Recent direct comparisons[33,40] have shown almost identical incidence of renal impairment with ACE inhibition compared to ARB therapy in CHF.

Aldosterone blockade

Aldosterone receptor blockade reduces mortality in chronic HF when used in combination with ACE inhibition,[12] or in HF associated with acute myocardial infarction (MI) in conjunction with both an ACE inhibitor and a beta blocker.[14] This clinical benefit may result from suppression of the effects of 'aldosterone escape' which is seen with chronic ACE inhibition. Aldosterone receptor antagonists are generally well tolerated[12,13] but by impairing the potent effect of aldosterone on potassium excretion, addition of an aldosterone receptor antagonist to ACE inhibitor therapy increases significantly the risk of hyperkalaemia.[12,13] Reciprocally, though, the incidence of hypokalaemia is reduced significantly (figure 2).[13] Hypokalaemia is a more common occurrence than hyperkalaemia in the absence of renal

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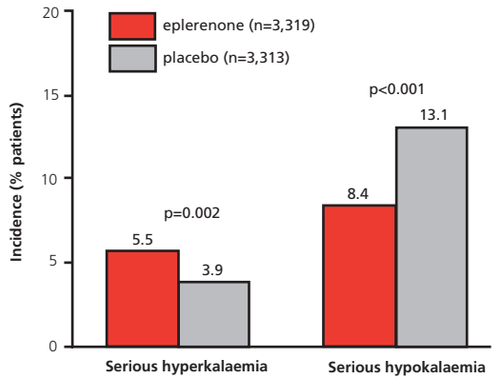
Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 4

Figure 2. Incidence of serious hyperkalaemia and serious hypokalaemia among 6,608 CHF patients randomised to the aldosterone receptor antagonist eplerenone or placebo. Serious hypokalaemia was defined as serum potassium ≥ 6 mmol/L. Serious hypokalaemia was defined as serum potassium < 3.5 mmol/L



Adapted from Pitt B *et al.*[13]

insufficiency, and the reduction in hypokalaemia seen with aldosterone blockade may contribute to the reduced risk of sudden cardiac death shown in recent trials with spironolactone[12] or eplerenone.[13]

Patients with advanced CHF who receive aldosterone blockade are already at relatively high risk of electrolyte abnormalities. As would be expected, the risk of hyperkalaemia with aldosterone blockade is higher among patients with renal dysfunction. In recognition of this, the major trials of aldosterone receptor antagonists in CHF excluded patients with renal insufficiency or raised serum potassium, and serum potassium levels were checked routinely during dose titration.[12,13] For patients with baseline creatinine clearance > 50 mL/min, there is little difference in incidence of hyperkalaemia with aldosterone blockade versus placebo.[13]

This has clear implications for the use of these agents in everyday clinical practice, where patients are more likely to have co-morbidity such as renal impairment. Aldosterone receptor antagonists should, accordingly, be used with great care in patients with moderate-to-severe renal insufficiency. For patients with mild renal impairment for whom aldosterone receptor antagonist therapy is indicated, concomitant use of potassium-sparing diuretics should be avoided. With these precautions, and by following recommended dosing guidelines, aldosterone blockers can be used with relatively low risk of hyperkalaemia.

It has been hypothesised that spironolactone could be associated with a higher risk of hyperkalaemia than epleronone due to longer half-life,[7] but this has not been assessed clinically.

Potassium monitoring in CHF

For patients with CHF, serum potassium levels of between 4.5–5.0 mmol/L[1] or 4.5–5.5 mmol/L[41] have been recommended. Intervention should certainly take place if values fall below 4.0 mmol/L. Levels above 5.5 mmol/L are to be avoided; as noted already, a high proportion of CHF patients have some degree of renal impairment and are vulnerable to hyperkalaemia.

Routine monitoring of serum potassium is a long-standing recommendation for CHF patients receiving an ACE inhibitor, ARB therapy or an aldosterone receptor antagonist. In patients who have normal or near-normal renal function and low baseline potassium, monitoring should be undertaken regularly as part of standard management. In patients with moderate renal failure or relatively high serum potassium, more frequent monitoring is necessary. The intensity of monitoring should be increased in the event of volume-depleting illness or deterioration of renal function. More intensive monitoring is also recommended in patients at high risk of renal impairment, e.g. diabetic patients and the elderly. It is worth bearing in mind that the early symptoms of clinically relevant hyperkalaemia, such as muscle weakness or myocardium conduction abnormalities, may be non-specific or may mimic those of advanced CHF. Monitoring by regular assessment of biochemistry will increase the chances of adverse changes being detected early.

Implications of hypokalaemia for CHF therapy

The response to a diagnosis of hypokalaemia must be dependent upon the clinical findings in the individual patient. As noted above, hypokalaemia may be a manifestation of fluid retention and increased diuresis may be required. On the other hand, the problem may be excessive diuresis. Careful assessment of the patient and the full biochemical picture will usually be required.

In clinical practice, the incidence of hypokalaemia may be higher in patients who are not taking either an ACE inhibitor or ARB, usually because of intolerance. In these individuals, hypokalaemia can be ameliorated by the introduction of an aldosterone receptor antagonist. More often, the patient is receiving an ACE inhibitor or an ARB; again addition of an aldosterone receptor antagonist may be appropriate.[42] If serum potassium is < 5.0 mmol/L and the patient is already receiving aldosterone blockade, careful increase in the dose is recommended. Increasing dietary intake of potassium[43,44] or use of potassium supplements[45] are less effective strategies, although dietary intake should be checked. Diuretic therapy is not associated with potassium loss in adrenalectomised patients, suggesting that the hyperaldosterone response to diuretic therapy, not the diuretic itself, induces kaliuresis. Accordingly, aldosterone blockade may be a more rational therapeutic choice than potassium supplementation in patients receiving loop or thiazide diuretics.[43] The minimum effective dose of loop or thiazide diuretic agents should be used. Switching from a loop to a potassium-sparing diuretic may be possible, particularly for those patients with low diuretic requirements. For those in whom continuing a loop diuretic is considered clinically necessary, addition of a small dose of a potassium-sparing diuretic may be appropriate. Since aldosterone receptor antagonists replenish tissue levels of both potassium and magnesium, these may be preferable to other potassium-sparing

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Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 5

diuretics.[41] Beta blockers counteract the hypokalaemic effect of catecholamines that is seen even in the presence of ACE inhibitor therapy and, as such, are thought to help reduce the risk of hypokalaemia-related arrhythmias and sudden cardiac death.

Implications of hyperkalaemia for CHF therapy

Hyperkalaemia may be a medical emergency. The urgency of intervention rises if other electrolyte irregularities are present, such as hyponatraemia, or if there are ECG abnormalities or arrhythmias. Intervention to reduce serum potassium levels $\geq$ 5.5 mmol/L is advisable, even if ECG readings are normal. Acute management techniques such as administration of intravenous calcium are familiar to most clinicians. Restriction of dietary potassium and withdrawal of potassium supplements are routine, and specific causes of hyperkalaemia should not be neglected – e.g. where hyperkalaemia occurs secondary to diabetes, antihyperglycaemic treatment can have a corrective effect.

Modifications to the CHF treatment regimen are likely to be required in order to achieve long-term stability of potassium levels. Such modifications should be approached carefully, and continuation of ACE inhibitor/ARB, beta blocker and aldosterone receptor antagonist therapy should be sought to avoid loss of their proven survival benefits. ACE inhibitors or ARBs may need to be temporarily discontinued to allow potassium levels to normalise, after which attempts should be made at reintroduction and upwards titration. It is possible that short-acting ACE inhibitors may be better tolerated than long-acting agents,[11] and there may be a benefit in selecting an ACE inhibitor that has significant hepatic clearance. If serum potassium exceeds 5.5 mmol/L, aldosterone receptor antagonists should be discontinued temporarily, or the dose reduced until the potassium level is in the range 4.5–5.5 mmol/L. Use of a loop diuretic in combination with metolazone enhances potassium excretion even when there is pronounced renal dysfunction, and may be helpful for hyperkalaemia in patients receiving an aldosterone blocker. Excessive diuretic therapy should be avoided.

Conclusion

Incorporating potassium homeostasis as an integral part of CHF management protocol offers the most effective means to protect patients from the risks of potassium imbalance and its potentially serious clinical sequelae. Avoiding hypokalaemia or hyperkalaemia is central to reduction of risk of ventricular abnormalities and sudden cardiac death in CHF patients. The clinician's quandary is that the very agents which confer significant mortality or symptomatic improvements in CHF also complicate potassium regulation. The benefits of diuretics in providing symptomatic relief, and the value of ACE inhibitors, ARBs and aldosterone receptor antagonists in improving outcomes are so well established that the clinical priority is to avoid long-term discontinuation of those therapies due to potassium imbalance. Prudent monitoring of potassium, modification of diuretic type and dose, possibly with addition of an aldosterone receptor antagonist, can avert clinically significant hypokalaemia. Similarly, routine potassium monitoring, identification of high-risk patients, and careful dose titration of neuroendocrine therapy minimises the risk of hyperkalaemia. Maintaining potassium balance is important in any circumstances, but becomes particularly critical in CHF, where mechanical, electrical and neuroendocrine forces combine to create a highly pro-arrhythmic environment.

Key messages

- Maintaining potassium homeostasis is a key part of chronic heart failure (CHF) management
- Both hypokalaemia and hyperkalaemia may increase risk of ventricular arrhythmias and sudden cardiac death
- Potassium levels should be maintained between 4.5 mmol/L and 5.5 mmol/L in patients with CHF
- Regular serum potassium monitoring should be routine practice, with increased frequency in high-risk patients
- Addition of a potassium-sparing diuretic, with preferential use of an aldosterone receptor blocker, can ameliorate hypokalaemia
- If temporary discontinuation of ACE inhibitor and aldosterone receptor antagonist is required in hyperkalaemia, attempts should be made to continue these in the long term if possible

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Conflict of interest

IS has served as Councillor on the Board of the British Society for Heart Failure. He has participated as a researcher in a number of trials in heart failure, received financial assistance with attendance at conferences from MSD, Roche, Pfizer and Astra-Zeneca, and received honoraria for speaking or consulting for MSD, Roche, Pfizer, Takeda and Astra Zeneca.

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Squire 224-229:Squire 224-229 8/6/05 5:55 pm Page 6

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