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Potassium and Heart Failure

Howard S. Rosman, MD,* Mihai Gheorghiade, MD,* and Sidney Goldstein, MD*

Chronic heart failure is as old as the human species. Successful interventions were made over two centuries ago with the promulgation by Withering of the Shropshire Lady’s use of foxglove in dropsy (1). One century ago, Ringer was the first to link changes in the concentration of the blood salts (potassium, calcium, and sodium) with alterations in numerous heart muscle functions including rhythmicity and irritability (2,3). In 1930 Sampson and Anderson reported successful abolition of atrial and ventricular ectopic beats and tachycardia in humans with doses of oral and intravenous potassium salts (4). More recently, the role of electrolyte disturbances in arrhythmias and sudden death has been a subject of intense scrutiny (5-7).

This paper explores the interrelationship of potassium abnormalities and heart failure regarding their association with and contributions to ventricular arrhythmias and sudden death. We will also discuss the electrophysiological basis by which potassium alterations cause arrhythmia; the role of magnesium; the direction of future studies; and the clinical recommendations for electrolyte monitoring in heart failure patients.

Electrolyte Abnormalities and Heart Failure

Hypokalemia and hypomagnesemia
In 1930 Harrison and colleagues demonstrated that heart failure patients had diminished body content of potassium (8). In subsequent years researchers unraveled the mechanism of potassium depletion. The reduction in cardiac output and increased peripheral resistance that commonly accompany heart failure lead to reduced renal plasma flow and stimulation of the renin-angiotensin system. Due to aldosterone and non-aldosterone mechanisms, sodium is avidly held by the kidneys at the expense of other cations, potassium and magnesium. As a result, patients with heart failure have marked deficits of potassium and magnesium. These deficits may not be apparent in serum measurements (9).

Plasma norepinephrine levels are increased in heart failure patients (10). This increase in norepinephrine appears to be proportional to the degree of symptoms rather than the severity of heart failure (11). Catecholamines, via a specific β₁-adrenoceptor effect, cause a further lowering of serum potassium (12). The link between catecholamines and hypokalemia is thus more intriguing since we know that plasma norepinephrine levels are important predictors of mortality in heart failure patients (13).

Diuretics and digitalis have been the mainstays of heart failure treatment since the 1950s. Diuretics directly cause increased renal excretion of potassium and magnesium and also induce hyperaldosteronism and metabolic alkalosis.

Hyperkalemia and hypermagnesemia
Elevated serum potassium levels resulting from oral potassium supplementation are not uncommon. Lawson et al reported that 3% of nearly 4,000 hospitalized patients with heart failure were hyperkalemic, whereas 5% of the patients were hypokalemic (14). Hollenberg and Bannon recently reported that hyperkalemia occurred in only 0.2% of 45,000 hypertensive patients treated with maxide, a new diuretic which combines thiazide with the potassium-sparing triamterene (15). Virtually all cases of hyperkalemia in heart failure patients are caused by potassium supplementation or potassium-sparing diuretics in combination with baseline renal insufficiency, diabetes, or other “potassium elevating” drugs such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory agents (14,15). A patient with stable serum potassium values rarely will become hyperkalemic abruptly as a result of worsening ventricular function with further depression of cardiac output (16). Both hypokalemia and hyperkalemia are seen in heart failure patients. Hypokalemia is mainly a physiologic response to congestive heart failure made worse by potassium-losing diuretics; hyperkalemia is almost always iatrogenic.

Electrolyte Abnormalities and Ventricular Arrhythmias
Sampson elegantly reviewed the series of discoveries in animals and man which linked depletion of potassium to ventricular arrhythmias, and repletion of potassium to arrhythmia abolition and, although rarely, to arrhythmia aggravation (2,17,18). More recently, the significance of diuretic-induced hypokalemia in hypertensive patients has been debated at great length and with much zeal (19-23).

Hypertensive patients
Diuretics have been the foundation of antihypertensive therapy. The benefit of these drugs in reducing mortality from stroke, renal failure, and chronic heart failure is generally accepted (23). Whether the diuretic-induced potassium loss causes arrhythmias, which pose a separate risk to the patient, has been hotly contested (24-27). The most comprehensive, current hypothesis is that hypertensive patients with evidence of organic
heart disease are at great risk of diuretic-associated ventricular ectopy, while hypertensive patients without evidence of heart disease are not at risk (28).

Acute myocardial infarction patients

Nordrehaug and colleagues have provided data which clearly show that hypokalemia is a risk factor for ventricular arrhythmias (29) and ventricular fibrillation (30) in the setting of acute myocardial infarction. In a prospective study of 60 patients with acute myocardial infarction, serum potassium as a continuous variable was inversely related to the incidence of unifocal ventricular ectopy and ventricular tachycardia. This relationship remained significant even after elimination of digitalis and left ventricular dysfunction by multivariate analysis (29).

In an earlier study of 1,074 patients with acute myocardial infarction, Nordrehaug and von der Lippe found that 17% of hypokalemic patients (potassium < 3.5 mmol/L) subsequently developed ventricular fibrillation compared to only 7% of normokalemic patients (30).

Heart failure patients with and without digitalis

It is well accepted that hypokalemia is associated with ventricular arrhythmias in digitalized patients (23,31,32). Patients with chronic heart failure historically have been treated with digitalis, but since digitalis is a highly toxic inotrope it is no longer prescribed routinely. Recent studies show that complex ventricular arrhythmias are present in heart failure patients even in the absence of digitalis (33-35). This led Packer et al to describe congestive heart failure as the “most arrhythmogenic disorder in cardiovascular medicine” (36). The importance of hypokalemia in ventricular arrhythmias in heart failure patients off digitalis has not yet been proven.

Electrolyte Abnormalities and Sudden Death

Scant information is available on the electrolyte status of humans just before sudden death. Surprisingly, not much data exist concerning serum electrolytes subsequent to sudden death. Thompson and Cobb examined electrolytes, blood gas values, and diuretic histories of 115 patients immediately after resuscitation from out-of-hospital ventricular fibrillation (37). They found serum potassium levels less than 3.6 mmol/L in 49% of these patients and hypokalemia in 19% of patients with acute myocardial infarction and 9% of ambulatory patients with coronary heart disease. Because no strong relationship between diuretic usage and hypokalemia was found, they concluded that hypokalemia may have occurred not preceding resuscitation but as a result of it. They speculated that bicarbonate therapy could have shifted potassium intracellularly without causing extracellular alkalosis.

Goldstein et al recently reported on 227 survivors of out-of-hospital cardiac arrest (38). Further analysis of the data revealed that 68% of the patients were hypokalemic (potassium < 3.6 mmol/L) within six hours of resuscitation. An additional 43 survivors of cardiac arrest showed no evidence of coronary artery disease. Among these survivors were 14 patients with dilated cardiomyopathy (Table). In this small subset, 11 patients (78%) were found to be hypokalemic postresuscitation. Furthermore, hypokalemia was present in seven of eight patients on diuretics (mean 3.2 mmol/L) and in four of six patients not on diuretics (mean 3.6 mmol/L).

Since Thompson and Cobb’s publication (37), the work of Brown et al (12) has indicated that catecholamines cause a significant decrease in serum potassium. The arrest itself leads to endogenous release of catechols, and epinephrine is frequently administered during resuscitation.

Hypokalemia is thus frequently present subsequent to cardiac arrest and resuscitation. It is tempting to speculate that it may be the mechanism of the arrest, but no data currently exist to confirm this hypothesis.

Importance of Electrolyte Abnormalities in Chronic Heart Failure

Sudden death occurs in nearly 40% of heart failure patients (6). Its incidence is equal to death secondary to progressive ventricular dysfunction. Sudden death is most commonly caused by ventricular tachycardia or fibrillation. Left ventricular dysfunction and ventricular arrhythmias act synergistically to determine subsequent mortality (6,39).

The aforementioned data strongly suggest that hypokalemia is associated with chronic heart failure and with arrhythmic sudden death in heart failure. The current question is whether it is important in causing sudden death.

Electrophysiology

A sound, theoretical basis exists for potassium to be an important contributor to ventricular arrhythmia (40). Ventricular tachyarrhythmias most often result from reentrant rhythm disturbances. Hypokalemia prolongs action-potential duration far more than it extends the refractory period. This imbalance establishes the milieu for unidirectional block and reentrant arrhythmias. This propensity for arrhythmia is heightened by the increased automaticity and decreased conductivity of ventricular tissue rendered hypokalemic.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum Potassium* (mmol/L)</th>
<th>pH (if present)</th>
<th>Digoxin</th>
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</table>

*Lowest recorded value in first six hours postresuscitation.
Clinical data

Hypokalemia can cause ventricular arrhythmia and death in heart failure patients on digitalis. Cohn et al speculated that the increase in plasma norepinephrine found in heart failure patients could be a cause of mortality (13). It is equally tenable that diuretics and increased norepinephrine may be the link between hypokalemia and death.

Hypothesis

No conclusive evidence exists regarding hypokalemia as an important independent contributor toward sudden death in patients with chronic heart failure. This conclusion would require a randomized, prospective study with a control group of hypokalemic heart failure patients not replenished with potassium. This study will never be performed. Therefore, clinicians must continue to weigh evidence and create hypotheses and treatment plans with available but incomplete information.

Until contrary information is available, it should be assumed that hypokalemia is an independent cause of death in heart failure patients whether hypokalemia is a result of diuretics or of the body’s compensatory response to decreased cardiac output with activation of the sympathetic nervous system and renin-angiotensin system.

Therapeutic Recommendations

All heart failure patients, not only those receiving digitalis preparations, should receive careful treatment when potassium levels fall below 3.5 mmol/L. Potassium repletion can be attained by potassium supplementation, potassium-sparing diuretics, and also by therapy with ACE inhibitors or beta blockers.

Vasodilators play an increasingly important role in the treatment of congestive heart failure patients. It was first suggested at a recent prospective trial that vasodilators prolong life in congestive heart failure patients (41). Angiotensin- converting enzyme inhibitors are potent vasodilators which serve to block aldosterone and reduce renal losses of potassium and magnesium. A randomized, blinded study showed that captoril reduced the incidence of ventricular ectopic beats and episodes of ventricular tachycardia in heart failure patients (42).

Beta blockers raise serum potassium and magnesium by blocking β1-receptor stimulation by catecholamines (12). These agents rarely alleviate symptoms in tachycardic congestive heart failure patients. Some investigators have reported improved mortality when sympatholytic drugs were used in congestive heart failure patients (43,44).

Theoretically, potassium-sparing diuretics may be preferable to potassium supplementation because they are better tolerated by patients and maintain body stores of magnesium.

As mentioned earlier, hypokalemia is often present simply as a physiologic response to congestive heart failure. However, hypokalemia is generally iatrogenic and life-threatening. It is essential that all patients at risk of hyperkalemia be carefully monitored. Contraindications to the use of potassium-repleting medications, such as renal insufficiency and diabetes mellitus, and various other drugs, including the nonsteroidal and anti-inflammatory agents, must not be overlooked.

References


25. Holland OB, Nixon J, Kuhnert LA. Diuretic-induced ventricular ec-


