Hypokalemia and sudden cardiac death

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Worldwide, approximately three million people suffer sudden cardiac death annually. These deaths often emerge from a complex interplay of substrates and triggers. Disturbed potassium homeostasis among heart cells is an example of such a trigger. Thus, hypokalemia and, also, more transient reductions in plasma potassium concentration are of importance. Hypokalemia is present in 7% to 17% of patients with cardiovascular disease. Furthermore, up to 20% of hospitalized patients and up to 40% of patients on diuretics suffer from hypokalemia. Importantly, inadequate management of hypokalemia was found in 24% of hospitalized patients. Hypokalemia is associated with increased risk of arrhythmia in patients with cardiovascular disease, as well as increased all-cause mortality, cardiovascular mortality and heart failure mortality by up to 10-fold. Long-term potassium homeostasis depends on renal potassium excretion. However, skeletal muscles play an important role in short-term potassium homeostasis, primarily because skeletal muscles contain the largest single pool of potassium in the body. Moreover, due to the large number of Na^+/K^+ pumps and K^+ channels, the skeletal muscles possess a huge capacity for potassium exchange. In cardiovascular patients, hypokalemia is often caused by nonpotassium-sparing diuretics, insufficient potassium intake and a shift of potassium into stores by increased potassium uptake stimulated by catecholamines, beta-adrenoceptor agonists and insulin. Interestingly, drugs with a proven significant positive effect on mortality and morbidity rates in heart failure patients all increase plasma potassium concentration. Thus, it may prove beneficial to pay more attention to hypokalemia and to maintain plasma potassium levels in the upper normal range. The more at risk of fatal arrhythmia and sudden cardiac death a patient is, the more attention should be given to the potassium homeostasis.

Key Words: *Arrhythmia; Hypokalemia; Na^+/K^+-ATPase; Potassium; Sudden cardiac death*

Worldwide, approximately three million people suffer sudden cardiac death (ie, death from heart disease within 1 h) annually. Of these, approximately 0.5 million people are younger than 50 years of age. Great progress has been achieved in the treatment of coronary artery disease, heart failure and arrhythmia over the past decades, but a fundamental breakthrough against sudden cardiac death is lacking. Thus, scientists and clinicians in the field of heart disease currently consider fighting sudden cardiac death to be the major challenge (1).

Sudden cardiac death emerges from a complex interplay of substrates and triggers. Structural abnormalities are substrates, and perturbations of the environment at the level of heart myocyte and Purkinje fibre membranes (eg, ischemia, electrolyte disturbances, autonomic changes and exercise) are triggers promoting arrhythmia, which may culminate in death. Disturbed potassium homeostasis among heart cells is such a trigger. Thus, hypokalemia and, also, more transient reductions in plasma potassium concentration are of importance.

Long-term (hours to days) potassium homeostasis depends on renal potassium excretion. However, several tissues contribute to transient short-term (seconds to minutes) potassium homeostasis. Here, skeletal muscles play an important role primarily because skeletal muscles contain the largest single pool of potassium in the body. Thus, for an adult human subject it can be calculated that the potassium content of the total skeletal muscle pool is approximately 225 times larger than the total potassium content in plasma. Moreover, due to the large number of Na^+/K^+-ATPase (also known as Na^+/K^+ pumps) and K^+ channels, the skeletal muscles possess a huge capacity for potassium exchange. Hence, for an adult human subject it can be calculated that if all Na^+/K^+ pumps are activated to maximum capacity for potassium uptake, the entire extracellular potassium pool can be cleared in less than 30 s. This mechanism can shift potassium from plasma to stores, causing hypokalemia within seconds to minutes (2).

TABLE 1
Common causes of hypokalemia in patients with cardiovascular diseases

Hypokalemia due to potassium depletion
Increased loss of potassium
Nonpotassium-sparing diuretics
Decreased intake of potassium
Malnutrition
Hypokalemia due to shift of potassium to stores
Stimulation of Na^+/K^+-ATPase (Na^+/K^+ pumps)
Catecholamines
Beta-adrenoceptor agonists
Insulin

The present article reviews hypokalemia and transient reductions in plasma potassium concentration in relation to the risk of sudden cardiac death.

HYPOKALEMIA DUE TO POTASSIUM DEPLETION

Hypokalemia is generally defined as a serum potassium concentration that is lower than 3.5 mmol/L. If plasma potassium is measured, the value should probably be slightly lower. This difference is due to release of potassium from platelets during clotting. Potassium depletion is generally defined as reduced total body stores. In cardiac patients, hypokalemia and potassium depletion are often caused by an increased loss of potassium through the kidneys due to nonpotassium-sparing diuretic therapy. This effect is, furthermore, often aggravated by insufficient potassium intake due to reduced appetite and the relatively low potassium content in modern food (Table 1).

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It has been known for nearly a century that cardiovascular diseases are associated with hypokalemia and potassium depletion in the heart (3). Moreover, large-scale studies from recent decades (4-8) including, in total, more than 13,000 patients have shown that hypokalemia is present in 7% to 17% of patients with hypertension, acute myocardial infarction and heart failure. Also, up to 20% of hospitalized patients and up to 40% of patients on diuretics suffer from hypokalemia (9). Whereas hypokalemia has been ignored by some investigators (10), the risk induced by hypokalemia in cardiac patients seems relatively well documented (11,12). Thus, in one study (13), the mortality rate of hospitalized hypokalemic patients was 10-fold higher than that of the general hospitalized population. Moreover, inadequate management of hypokalemia was found in 24% of these cases. In hypertension, diuretic therapy is associated with an increased risk of cardiac arrest and death (14,15). Nonpotassium-sparing diuretic therapy for hypertension increased ventricular ectopic activity – an effect that was abolished by potassium repletion obtained by shift to, or addition of, potassium-sparing spironolactone (16). Also in hypertension, thiazide diuretics increased ectopic ventricular activity during exercise (17). In myocardial infarction, hypokalemia was associated with an increased risk of ventricular tachycardia and ventricular fibrillation. Thus, the incidence of ventricular fibrillation has been found to be fivefold higher in patients with a low serum potassium concentration than in patients with a high serum potassium concentration. Moreover, no episodes of ventricular fibrillation were observed in patients with serum potassium concentrations of greater than 4.6 mmol/L. Also, the incidence of ventricular tachycardia has been found to correlate negatively with plasma potassium concentration. Within the range for normal serum potassium concentration, the risk was increased threefold for patients with low serum potassium concentration compared with patients with high serum potassium concentration (18-22). In heart failure, hypokalemia was an independent risk factor for reduced survival (7,23). In general, the lower the plasma potassium concentration, the higher the risk. In a recent re-evaluation of 7788 patients with heart failure (8), matched HRs for patients with serum potassium concentrations of lower than 4 mmol/L compared with matched patients with serum potassium concentrations in the range of 4.0 mmol/L to 4.9 mmol/L were 1.56 for all-cause mortality, 1.65 for cardiovascular mortality and 1.86 for heart failure mortality ($P<0.0001$). It is of interest that drugs with a proven significant positive effect on mortality and morbidity rates in heart failure patients all increase plasma potassium concentration: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (23,24), beta-adrenoceptor antagonists (25) and the aldosterone antagonist spironolactone (26). Moreover, another recent re-evaluation of 7788 patients with heart failure (27) indicated that potassium supplements eliminated the increased mortality associated with hypokalemia.

Much of the knowledge regarding the mechanisms involved in hypokalemia and potassium depletion comes from physiological studies using experimental animal and human models. Due to the danger of hypokalemia, it should not be induced experimentally in human subjects, but may be studied in experimental animals. Moreover, it may also be studied in patients undergoing standard potassium repletion as therapy for accidental hypokalemia. Rats that were potassium depleted by potassium-deficient fodder or nonpotassium-sparing diuretics showed that potassium was initially lost from plasma and skeletal muscles. Skeletal muscle acts as a reservoir pool for potassium, maintaining potassium in vital organs such as the heart and brain. The loss of potassium from skeletal muscles seems to be due to a reduced concentration of Na^+/K^+ pumps, decreasing the capacity for potassium uptake (28-30). Interestingly, in a study of heart failure patients prescribed nonpotassium-sparing diuretics and potassium supplements (31), both skeletal muscle potassium and Na^+/K^+-ATPase concentrations were reduced, even though plasma potassium was maintained in the normal range. This indicates that in the initial phase of potassium depletion, potassium is primarily lost from skeletal muscles, maintaining plasma potassium. Later, potassium is lost from plasma and muscles, and finally, from other compartments, resulting in potassium concentrations so low that life becomes unsustainable. When rats were readministered potassium, plasma and skeletal muscle stores were almost immediately repleted (28,29). However, it took days before the skeletal muscle Na^+/K^+ pump concentration was restored. In the rat heart, the reduction in potassium content was much lower than in skeletal muscles, and heart muscle Na^+/K^+ pump content initially showed a small upregulation, later followed by a reduction; however, this reduction was much smaller than in skeletal muscles (32,33). To some extent, these mechanisms are probably, for some time, protective against the development of dangerous arrhythmia during mild hypokalemia and potassium depletion.

HYPOKALEMIA DUE TO SHIFT OF POTASSIUM INTO STORES

Shift of potassium into stores may cause a rapid reduction in serum potassium concentration to below 3.5 mmol/L. This may result from stimulation of the activity of Na^+/K^+ pumps in skeletal muscles. Thus, potassium is transferred from plasma to skeletal muscle cells. This type of hypokalemia can arise and vanish within seconds to minutes due to the huge capacity of skeletal muscle Na^+/K^+ pumps and K^+ channels. Because it occurs without any potassium depletion, it is sometimes called pseudohypokalemia to distinguish it from hypokalemia associated with potassium depletion. In cardiac patients, this hypokalemic effect of beta-adrenoceptor agonists as well as its inhibition by beta-adrenoceptor antagonists is of major interest. Also, insulin's hypokalemic effect is of interest because these patients often have diabetes as a comorbidity (Table 1).

Injection or inhalation of a beta-adrenoceptor agonist in therapeutic doses reduces plasma potassium concentration in healthy subjects by as much as 1.5 mmol/L (34,35). Moreover, an overdose of beta-adrenoceptor agonists may reduce plasma potassium concentration to 2.2 mmol/L (36,37). A relatively recent meta-analysis (38) of six single-dose, placebo-controlled studies of 168 patients receiving beta-adrenoceptor agonists for asthma showed reductions in potassium levels by 0.23 mmol/L to 0.58 mmol/L (mean 0.36 mmol/L; 95% CI 0.18 mmol/L to 0.54 mmol/L). In one study (39), the reduction in potassium level by 0.58 mmol/L was associated with a prolongation in the electrocardiogram of the corrected QT (QTc) interval by 78 ms and an increase in heart rate by 61 beats/min. Because prolonged

QTc interval reflects abnormal cardiac repolarization, it is a predictor of dangerous arrhythmia, and there is speculation that severe hypokalemia is involved in some cases of sudden death among asthmatic patients. In addition, many diseases are associated with increased catecholamine levels that may also cause hypokalemia. This is evident from the hypokalemia occasionally seen in acute myocardial infarction (18-22). Importantly, hypokalemia is prevented in such patients treated with beta-adrenoceptor antagonists (40). Also, in heart failure, catecholamine levels are often increased, which may also induce hypokalemia and ventricular fibrillation (41). This may be especially dangerous if the hypokalemia adds to a pre-existing hypokalemia and/or potassium depletion from diuretic therapy for hypertension or heart failure. Also, insulin promotes hypokalemia. Thus, insulin-glucose infusion is standard acute therapy for the treatment of hyperkalemia. Moreover, an insulin overdose may cause dangerous hypokalemia (42). Also, an oral glucose load may increase plasma insulin and cause hypokalemia (43). Hyperinsulinemic clamping in humans resulted in hypokalemia and prolongation of heart repolarization (QTc interval prolongation shown in the electrocardiogram) that were prevented by beta-adrenoceptor antagonists (44). Thus, there is speculation that severe hypokalemia is involved in sudden cardiac death of diabetic patients during hypoglycemia. Indeed, many triggers may be involved – insulin, catecholamines and pre-existing hypokalemia and/or potassium depletion from nonpotassium-sparing diuretic therapy for hypertension or heart failure.

The mechanisms involved in the hypokalemic effects of beta-adrenoceptor agonists and insulin are well described. Thus, beta-adrenoceptor agonists stimulate Na^+/K^+ pump-mediated potassium uptake in skeletal muscles of experimental animals and humans (45-47). Likewise, insulin has been shown to increase skeletal muscle Na^+/K^+ pump-mediated potassium uptake (48,49). Interestingly, the combination of albuterol and insulin in patients with renal insufficiency showed an additive hypokalemic effect (50). On the other hand, another study showed that protection against insulin induced a further reduction in plasma potassium concentration in hypokalemia (51,52).

CONCLUSION

Recognizing plasma potassium dynamics and that hypokalemia is common and is often inadequately managed, it may be beneficial to pay more attention to hypokalemia and to maintain plasma potassium levels in the upper normal range. This may be of special importance in patients with cardiovascular diseases such as hypertension, coronary artery disease, heart failure and arrhythmia, especially if treated with nonpotassium-sparing diuretics, beta-adrenoceptor agonists and/or insulin. The more at risk of fatal arrhythmia and sudden cardiac death a patient is, the more attention should be given to the potassium homeostasis.

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