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Arrhythmias caused by Hypokalemia and Heart Failure: New Insights and Therapeutic Implications

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Abstract

Because of the widespread use of diuretics and neuro humoral activation, hypokalemia is a common electrolyte disorder among heart failure patients, contributing to an increased risk of ventricular arrhythmias and sudden cardiac death. Recent experimental studies suggest that hypokalemia-induced arrhythmias are initiated by decreased Na+/K+ATPase activity, which then leads to Ca2+ overload, Ca2+/Calmodulin-dependent kinase II (CaMKII activation, and the development of afterdepolarizations). The current mechanistic evidence of hypokalemia-induced triggered arrhythmias is reviewed in this article, and we discuss how molecular changes in heart failure may lower the threshold for these arrhythmias. Finally, we discuss how recent discoveries regarding hypokalemia-induced arrhythmias may have implications for future antiarrhythmic treatment strategies.

Introduction

Despite ongoing therapeutic advances, the long-term prognosis for Heart Failure (HF) remains poor, with overall 5-year mortality reaching 50%, and even higher in more advanced stages. SCD, most commonly caused by Ventricular Tachyarrhythmias (VTs), accounts for 50% of all HF deaths. Hypokalemia is a well-known risk factor for VT, and it is associated with worse clinical outcomes in HF patients, as well as an increased risk of ventricular arrhythmias and mortality during acute myocardial infarction. Although serum K+ levels are defined as hypokalemia, several studies show an increased risk of SCD and all-cause mortality in HF patients with serum-(K+) 4 mM. Depending on the definition of hypokalemia and patient characteristics, the prevalence of hypokalemia in HF patients ranges from 19% to 54%. Because all of these drugs increase serum K+ levels and thus counteract hypokalemia, the prevalence was more likely to be higher in patient populations studied before the introduction of beta-blockers, ACE inhibitors, and AT1 antagonists as standard HF therapy. Furthermore, the prevalence of hypokalemia is higher in hospitalized patients than in non-hospitalized patients. The most common causes of hypokalemia in heart failure are diuretics and activation of the renin-angiotensin-aldosterone system, which causes K+ loss in the urine. Increased catecholamine levels also help by shifting K+ into the intracellular compartment, whereas volume overload in more advanced HF may cause a dilution effect.

Diuretics, both thiazides and loop diuretics, have long been known to increase the risk of hypokalemia and cardiac arrhythmias in patients receiving digitalis. In the Multiple Risk Factor Intervention Trial, hypertensive men with baseline ECG abnormalities who received an intensive diuretics regimen had increased mortality compared to the standard regimen. Later trials found no increased mortality with intensive diuretic treatment or when comparing diuretics to other anti-hypertensive agents, leading some authors to argue that diuretics' anti-hypertensive effect compensates for the pro-arrhythmic effect of diuretics alone.

Nonetheless, one study found that a subset of thiazide users developed severe hypokalemia and cardiac arrhythmias, and a Case-Control study discovered a dose-response relationship between thiazide dosage and the risk of SCD. Importantly, diuretics were associated with a 30%-40% increased risk of arrhythmic death in patients with left ventricular dysfunction. Mineralocorticoid receptor antagonists, in contrast to thiazides and loop diuretics, limit renal excretion of K+, increase serum-(K+), and reduce the risk of cardiac arrhythmias caused by hypokalemia. ACE inhibitors, aldosterone receptor blockers, and beta blockers may be able to prevent hypokalemia by counteracting the neuro humoral activation associated with HF, which lowers serum-(K+).

Serum K+ levels change during and after intense exercise. Due to the release of K+ from skeletal muscles during exercise, marked hyperkalemia may develop. Increased catecholamine levels reduce recovery time from exercise-induced hyperkalemia by stimulating Na+/K+-ATPase. Surprisingly, serum-(K+) decreases during the recovery phase following physical exercise, resulting in post-exercise hypokalemia. The combination of hyperkalemia and subsequent hypokalemia during physical exercise, along with increased catecholamines, may contribute to the increased risk of cardiac arrhythmias and SCD observed during exercise in patients with structural or ischemic heart disease. Surprisingly, the risk of arrhythmias is highest during the recovery phase following exercise, which coincides with post-exercise hypokalemia. DADs are induced by spontaneous Ca2+ waves activating an inward current primarily composed of INCX. Because NCX is usually upregulated in HF, a given amount of spontaneously released Ca2+ generates a more depolarizing inward current, lowering the DAD threshold. During the resting phase of the AP, IK1 acts as a "safety valve," counterbalancing depolarizing inward currents caused by spontaneous Ca2+ release. In HF, IK1 is downregulated, increasing the likelihood of a spontaneous AP via the generation of EADs and/or DADs. In line with the typical observation of prolonged APD and reduced repolarization reserve, there is likely a lower threshold for hypokalemia-induced afterdepolarizations in HF, in addition to the previously described factors that may contribute to Na+ and Ca2+ overload in HF.

There is currently no treatment that directly targets the underlying mechanism of hypokalemia-induced arrhythmias. The current treatment for hypokalemia is potassium replacement, and magnesium sulfate injection is used to prevent EADs and DADs in patients with TDP via an unknown mechanism. To shorten the APD, TDP can also be treated with cardiac pacing or isoproterenol injection. New hypokalemia-induced arrhythmia treatments should ideally aim to (1) prevent EADs/DADs, (2) shorten the APD, and (3) directly target the underlying mechanism. Based on the model for hypokalemia-induced ventricular arrhythmias, we propose that CaMKII inhibition, NKA activation, and especially NKA2 activation be investigated further as future antiarrhythmic strategies. In addition to hypokalemia-induced VT/VF, CaMKII inhibition prevents hypokalemia-induced EADs, Ca2+ overload, and DADs in Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and HF. CaMKII inhibition also reduces APD, though this effect may vary depending on the species. There is currently no drug that specifically activates the NKA. In theory, because NKA inhibition causes Ca2+ overload, after depolarizations, and ventricular arrhythmias, this could be an effective antiarrhythmic strategy.APD prolongation and an increased risk of afterdepolarizations are also characteristics of HF, and we speculate that CaMKII inhibitors and NKA activators may be future antiarrhythmic options in HF even in the absence of hypokalemia.

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