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STATE-OF-THE-ART PAPER

What Is the Optimal Serum Potassium Level in Cardiovascular Patients?

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Humans are prone to sodium overload and potassium depletion. This electrolyte imbalance is important in the pathogenesis of cardiovascular disease and sudden cardiac death. Avoiding hypokalemia is beneficial in several cardiovascular disease states including acute myocardial infarction, heart failure, and hypertension. The evidence highlighting the importance of potassium homeostasis in cardiovascular disease and possible mechanisms explaining potassium's benefits are reviewed. Targets for serum potassium concentration are suggested. (J Am Coll Cardiol 2004; 43:155–61) © 2004 by the American College of Cardiology Foundation

Humans evolved ingesting a potassium-rich, sodium-poor diet, and mechanisms developed to retain sodium and excrete potassium (1). The sodium-rich diet of modern humans produces sodium overload and potassium depletion (2). Hypokalemia contributes to the pathogenesis of cardiovascular disease, and many cardiovascular disorders and drugs aggravate hypokalemia (3,4). Hypokalemia is therefore a common, reversible factor in the natural history of cardiovascular disease. This article will discuss potassium balance in cardiovascular disorders.

Potassium homeostasis. Potassium homeostasis is achieved by renal excretion matching oral intake (50 to 150 mmol/day). Virtually all filtered potassium is resorbed in the proximal convoluted tubule. The remainder is crucial because potassium excretion is dependent on the distal nephron's secretory mechanism. This is affected by tubular (flow and sodium delivery) and peritubular factors (serum potassium concentration, serum pH, and hormonal regulation). Aldosterone and vasopressin stimulate potassium secretion (and sodium resorption) by upregulating the abluminal sodium-potassium-ATPase pump and opening luminal sodium and potassium channels.

Total body potassium is 3,500 mmol, with 98% intracellular. Serum potassium is maintained between 3.5 and 5.3 mmol/l by renal excretion and shift between intracellular and extracellular fluid compartments. The sodium-potassium-ATPase pump preserves a high intracellular potassium concentration despite an adverse concentration gradient. It is stimulated by hyperkalemia, aldosterone, catecholamines, and insulin (5).

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PROTECTIVE EFFECTS OF POTASSIUM IN EXPERIMENTAL STUDIES

Cardiac effects. ARRHYTHMIA PROTECTION. Resting transmembrane potential difference depends on intracellular and extracellular potassium concentrations (Table 1). Hypokalemia causes cellular hyperpolarity, increases resting potential, hastens depolarization, and increases automaticity and excitability (6,7). Because cardiac repolarization relies on potassium influx, hypokalemia lengthens the action potential and increases QT dispersion (reflecting electrical inhomogeneity). Hypokalemic ventricular ectopy is suppressed by potassium replacement (8–10). Thus, hypokalemia increases risk of ventricular arrhythmia and sudden cardiac death (SCD) (3).

POTASSIUM AND DIGOXIN. Hypokalemia predisposes to digitoxicity by reducing renal clearance and promoting myocardial binding of the drug (11,12).This produces increased automaticity and ventricular arrhythmias (13). Hyperkalemia depolarizes myocytes and exacerbates digoxin's atrioventricular nodal blocking (14). Hypomagnesemia reduces intracellular potassium by reducing the membrane concentration of the sodium-potassium-ATPase pump and, thus, predisposes to digitoxicity. Hypokalemia and hypomagnesemia should be avoided in patients taking digitalis.

DIASTOLIC DYSFUNCTION. Potassium depletion produces diastolic dysfunction in animal and human models (15).

Vascular effects. ENDOTHELIAL FUNCTION. Experimentally, high potassium protects against hypertensive and sodium-induced endothelial dysfunction independent of blood pressure (BP) (16–21). In humans, intravenous potassium ameliorates hypertensive endothelial dysfunction (22). This effect is blunted by the competitive nitric oxide (NO) synthase inhibitor, N-monomethyl-L-arginine, implicating the NO pathway. Potassium partly mediates vasodilation via strong inwardly rectifying potassium channels and the sodium-potassium-ATPase pump of vascular

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AMI = acute myocardial infarction
BP = blood pressure
ECG = electrocardiogram/electrocardiographic/electrocardiography
HF = heart failure
LVH = left ventricular hypertrophy
MRFIT = Multiple Risk Factor Intervention Trial
NO = nitric oxide
RAAS = renin-angiotensin-aldosterone system
SCD = sudden cardiac death
VF = ventricular fibrillation
VSMC = vascular smooth muscle cell

smooth muscle cells (VSMCs) (23). This may be important when NO bioavailability is low. Potassium also blunts angiotensin-II–induced vasoconstriction (24,25). It is increasingly apparent that endothelial dysfunction is associated with a worse prognosis in cardiovascular disease (26,27).

THROMBOGENESIS AND PLATELET AGGREGATION. In vitro, high extracellular potassium concentration impairs platelet aggregation (28). In animal models, increasing plasma potassium reduces the rate of thrombosis on endothelial lesions (28). These effects occur with physiologically relevant increases.

ATHEROSCLEROSIS. Increasing dietary potassium reduces neointimal formation after angioplasty and reduces atherosclerotic load (28). Potassium ameliorates oxidative stress by reducing free-radical formation, impairing VSMC proliferation, and reducing monocyte adherence to vessel walls (28). Thus, potassium retards the progression of atherosclerosis.

Protective effects of potassium in clinical studies. AMI. Ischemic myocardium extrudes potassium, causing hypopolarization and reducing the arrhythmic threshold (29–31). Ventricular arrhythmia aggravates the hypopolarization and further lowers the arrhythmic threshold (32).

Table 1. Experimental Evidence for Beneficial Effects of Potassium

Cardiac	
Anti-arrhythmic	↓ Action potential duration
	↓ Electrical inhomogeneity
	↓ Risk of digoxin toxicity
Diastolic function	Hypokalemia worsens diastolic function
Vascular	
Vasomotor	Endothelial-dependent vasodilator
VSMC	↓ VSMC proliferation
Thrombosis	↓ Thrombus formation and platelet activation
Atherosclerosis	↓ Neointimal proliferation
	↓ Atherosclerotic lesion formation
	↓ Free radical generation

VSMC = vascular smooth muscle cell.

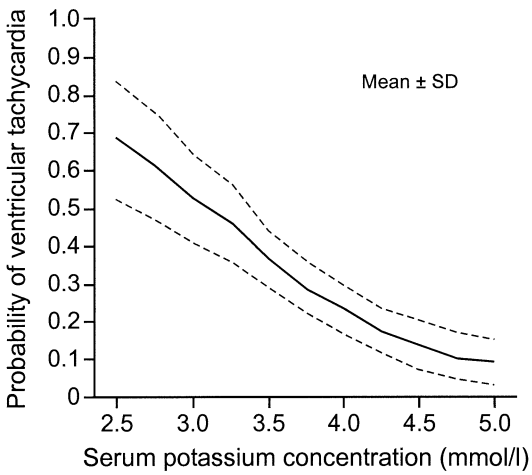

Figure 1. Probability of ventricular tachycardia in relation to serum potassium concentrations (40).

Adrenaline stimulates the sodium-potassium-ATPase pump via beta$_2$-receptors and shifts potassium intracellularly (33). The catecholamine surge that accompanies acute myocardial infarction (AMI) causes redistributional hypokalemia and hyperpolarizes non-ischemic myocardium, producing electrical inhomogeneity and ventricular arrhythmias. Potassium repletion abolishes these effects (34).

Clinical observations suggest that these mechanisms are important. Serum adrenaline levels are inversely correlated with serum potassium in AMI and are higher in SCD victims (35,36). Beta-blockers lessen hypokalemia in AMI, and this may partly explain their benefit (35,37). Hypokalemia is associated with ventricular fibrillation (VF) in AMI independent of diuretic usage (Fig. 1, Table 2) (38–41). Hulting et al. (39) found an inverse relationship between serum potassium and VF incidence. None occurred when serum potassium was over 4.6 mmol/l.

Hypokalemia due to prior non-potassium-sparing diuretic use results in more pronounced hypokalemia during AMI (42). Therefore, it seems sensible to avoid unopposed non–potassium-sparing diuretics in patients at risk for AMI. The effect of angiotensin-converting enzyme (ACE) inhibitors on mortality when started soon after AMI further support the evidence that normokalemia is beneficial in AMI (43).

Table 2. Serum Potassium Concentration Upon Hospital Admission and Risk of Early VF in AMI (39)

Incidence of VF (%)	Serum Potassium Concentration (mmol/l)
8	<3.5
4	3.5–3.8
2	3.9–4.2
1	4.3–4.6
0	>4.6

AMI = acute myocardial infarction; VF = ventricular fibrillation.

HYPERTENSION. Populations ingesting potassium-rich diets exhibit lower rates of hypertension than Western populations. Meta-analysis of randomized controlled trials of potassium supplementation in hypertension demonstrated significant reductions in systolic (−3.11 mm Hg) and diastolic (−1.97 mm Hg) BP (44). In the Dietary Approaches to Stop Hypertension trial, a potassium-rich diet resulted in BP reduction comparable with pharmacologic monotherapy (45). Several large studies have shown an inverse relationship between BP and potassium intake (46–48). This antihypertensive effect may be mediated by increased natriuresis, vasodilation, heightened baroreflex sensitivity, and reduced cardiac sensitivity to catecholamines and angiotensin II (49). The ratio of sodium excretion to potassium excretion is more closely related to BP than either measure individually (47,50). Interventions that increase sodium excretion while conserving potassium may, therefore, be particularly effective treatment for hypertension.

Diuretics inhibit chloride-dependent sodium resorption and induce potassium excretion in a dose-dependent manner (51). In hypertensives, reductions in serum potassium and magnesium correlate with increased ventricular arrhythmia, and thiazides increase SCD (52–55). A total of 7.2% of subjects taking chlorthalidone in the Systolic Hypertension in the Elderly Program were hypokalemic. They lost the cardioprotective benefit of BP reduction and demonstrated higher cardiovascular event rates than placebo (56). In the Multiple Risk Factor Intervention Trial (MRFIT), a 1 mmol/l reduction in serum potassium produced a 28% increase in ventricular arrhythmias (57). Subjects in MRFIT who were receiving higher doses of diuretics had increased risk of SCD, especially those with electrocardiographic (ECG) left ventricular hypertrophy (LVH) (57,58). Concurrent potassium-sparing diuretic treatment offsets these effects (52,53). Thiazides increase SCD compared with beta-blockade, but combining a thiazide with a potassium-sparing diuretic reduces the risk of SCD more than a beta-blocker (53) (Fig. 2). In elderly hypertensives, this combination reduced the risk of SCD by two-thirds (59).

Some workers have found no relationship between serum potassium and ventricular ectopy (60–62). However, these were small studies, and treatment was for four weeks, compared with 24 to 40 weeks for positive studies. Duration of treatment is crucial, as demonstrated by the Medical Research Council hypertension trial, in which ventricular ectopy was unaffected by thiazide therapy after two months, but was increased after two years and was related to hypokalemia (54).

The MRFIT data also suggest that hypokalemia increases SCD in hypertensives only if they are taking diuretics (57). This implies that renin-angiotensin-aldosterone system (RAAS) activation is required. Because of aldosterone's obligatory role in kaliuresis, aldosterone antagonism is effective in preventing diuretic-induced hypokalemia (63).

The above data provide persuasive evidence that avoiding hypokalemia in hypertensives is desirable. The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial results appear to contradict this (64). Mortality was not significantly different between the chlorthalidone and lisinopril groups despite a higher prevalence of hypokalemia in the diuretic-treated group. However, mean systolic pressure was 2 mm Hg lower in the chlorthalidone group, and this makes interpretation difficult.

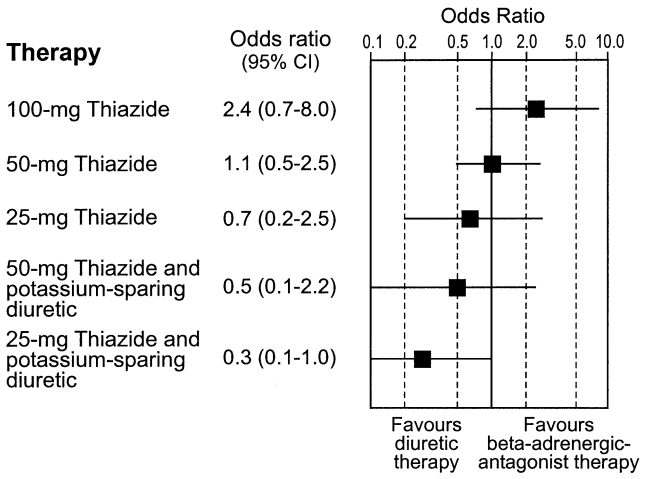

Figure 2. Risk of primary cardiac arrest associated with thiazide therapy with and without potassium-sparing diuretic therapy, as compared with beta-adrenergic-antagonist therapy, among patients treated with single anti-hypertensive drugs (53). Odds ratios are adjusted for age, gender, pretreatment systolic blood pressure and heart rate, duration of hypertension, current smoking, and diabetes mellitus. CI = confidence interval.

The Losartan Intervention for Endpoint Reduction in Hypertension study compared losartan with atenolol in the treatment of hypertensives with ECG LVH (65). Despite similar BP reductions in both arms, there was a reduction in the primary composite end point of cardiovascular death, stroke, and AMI in the losartan group. Interestingly, most patients in both groups were also taking chlorthalidone, and serum potassium fell slightly in the atenolol arm. One of the mechanisms of benefit may therefore have been prevention of hypokalemia. Hyperkalemia may increase cardiovascular risk in hypertensives, but this could reflect poor renal function (66). Overall, it seems prudent to avoid hypokalemia in hypertensives.

HEART FAILURE. Hypokalemia is a strong independent predictor of mortality in heart failure (HF) (67). Heart failure activates the RAAS and sympathetic nervous system and induces hypokalemia. Diuretics aggravate hypokalemia and heighten neurohormonal activation (68–70). Plasma and muscle magnesium and potassium concentrations are reduced in HF (71–73). Serum potassium is negatively correlated with plasma renin activity and plasma noradrenaline, and patients who respond to treatment show increases in intracellular potassium concentrations (25,74,75). Thus, neurohormonal activation contributes significantly to potassium depletion in HF.

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Table 3. Relative Risk of Arrhythmic Death According to Diuretic Use on Multivariate Analysis in Patients With Left Ventricular Dysfunction (79)

	RR (95% CI)	p Value
No diuretic	1.00	
Any diuretic	1.37 (1.08–1.73)	0.009
Non–potassium-sparing diuretic	1.33 (1.05–1.69)	0.02
Potassium-sparing diuretic	0.90 (0.61–1.31)	0.6

CI = confidence interval; RR = relative risk.

Most HF patients have increased ventricular ectopy, and 50% exhibit non-sustained ventricular tachycardia (76). A total of 50% of HF deaths are sudden, presumably due to malignant arrhythmias. In SCD victims, myocardial potassium is significantly lower than in controls, and survivors are often hypokalemic (77,78). In HF, all-cause and cardiac mortality rates are higher in individuals taking non–potassium-sparing diuretics (79). Incidence of arrhythmic death is significantly and independently related to use of non–potassium-sparing diuretics (Table 3).

By contrast, ACE inhibitors and aldosterone blockers (which increase serum potassium) improve prognosis (43,80–83). In class I to III HF, a lower serum potassium concentration (4.1 mmol/l vs. 4.4 mmol/l) is an independent predictor of sudden death (84). Elevation of potassium within the physiologic range in HF patients reduces QT, QTc, and QT dispersion (85). The mortality benefit of ACE inhibitors is probably partly due to increased serum potassium and ventricular arrhythmia reduction (43,80,81). The ACE inhibitors transiently suppress the RAAS, but high aldosterone levels and "ACE escape" frequently occur (86). A serum potassium increase of 0.25 mmol/l elevates serum aldosterone concentrations by 50% to 100% (87). Aldosterone antagonists are thus effective in raising serum potassium when the RAAS is activated.

Furthermore, concurrent repletion of magnesium with potassium with aldosterone blockade increases cellular potassium uptake and replenishes tissue levels of both cations (88). Potassium supplements and other potassium-sparing diuretics do not confer the same benefits (53,89). Therefore, aldosterone-blockers should be used in HF in preference to other potassium-sparing diuretics. Plasma catecholamine concentrations are powerful independent predictors of mortality even with concurrent ACE inhibitor therapy (90,91). As noted, catecholamines produce hypokalemia and increase arrhythmic risk. It seems likely that the observed mortality benefit with beta-blockade in HF is partly due to prevention of hypokalemic arrhythmias (92–94).

The evidence is persuasive that serum potassium level should be kept above 4 mmol/l in HF.

STROKE. High potassium intake reduces stroke risk independently of BP. A 10 mmol increase reduces relative risk by 40% (20,95–97). However, potassium-rich diets tend to be low in sodium and high in anti-oxidants, fiber, and magnesium, confounding the issue.

Table 4. Clinical Evidence for Beneficial Effects of Potassium and Recommended Targets for Serum Potassium Concentration in Cardiovascular Disorders

Disorder	Recommended Level	Evidence
Hypertension	3.5–5.0 mmol/l	High K^+ diet ↓ BP Hypokalemia ↑ ventricular arrhythmia
Stroke	Unknown	High K^+ diet ↓ risk of stroke
Acute MI	4.5–5.5 mmol/l	Hypokalemia ↑ ventricular arrhythmia
Heart failure	4.5–5.5 mmol/l	Hypokalemia ↑ ventricular arrhythmia Increasing serum K^+ ↓ ventricular arrhythmia and ↓ QT and QT_d Serum K^+ level is inversely related to prognosis

BP = blood pressure; MI = myocardial infarction.

MAGNESIUM. Hypomagnesemia occurs in primary hyperaldosteronism, and exogenous aldosterone increases magnesium excretion (98,99). Thus, hyperaldosteronism causes hypomagnesemia. Diuretics and digoxin also cause magnesium wasting (100–104). Therefore, in HF and hypertension, magnesium depletion is common. Hypomagnesemia increases potassium excretion, and hypokalemia is difficult to remedy with concurrent hypomagnesemia because the sodium-potassium-ATPase pump requires the presence of magnesium ions (105,106). Hypomagnesemia increases ventricular ectopic activity and is related to prognosis in HF (107). This may be partly due to potassium depletion (79). Potassium-sparing diuretics prevent urinary magnesium wasting (100).

Hypomagnesemia should be remembered as a cause of refractory hypokalemia.

Conclusions and recommendations. Several large, well-designed clinical trials have implicated hypokalemia and thiazide diuretic use as risk factors for SCD (45,53,56–59). However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) data have cast doubt on this assertion (64). Despite this, hypokalemia should be avoided, especially with co-existing coronary artery disease or HF (65).

The data linking hypokalemia with arrhythmia and cardiac arrest in AMI are fairly strong, but the direct myocardial effect of increased circulating adrenaline is a possible confounder (38,39). Despite this, it is sensible to maintain a serum potassium concentration above 4.5 mmol/l during AMI.

In HF, there is increasing evidence that the serum potassium level should be maintained above 4.5 mmol/l to minimize the risk of SCD (79,82–84). Adding spironolactone to standard therapy of a loop diuretic and an ACE inhibitor or angiotensin II receptor blocker where serum

potassium remains below 4.0 to 4.5 mmol/l is now mandatory in class III to IV HF and may also be advisable in classes I to II. Potassium supplements and other potassium-sparing diuretics do not confer the same benefit as spironolactone and appear ineffective due to poor compliance and lack of magnesium repletion (53,89). Following the Valsartan Heart Failure Trial (VALHEFT) results, an angiotensin II receptor blocker should also be considered (108). The available stroke data are more preliminary, and effects are confounded by dietary factors.

It is desirable to avoid hypokalemia in cardiovascular patients. In AMI and HF, it seems beneficial to aim for serum potassium levels above 4.5 mmol/l (Table 4). It is unknown whether serum potassium levels 5.5 to 6.5 mmol/l without hyperkalemic ECG changes are beneficial. It would appear wise to avoid potassium levels above 5.5 mmol/l, especially in the community, as these patients often have a degree of renal impairment and are at risk for frank hyperkalemia with dietary changes, dehydration, and intercurrent illness.

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