

Electrolyte disorders and arrhythmogenesis

Nabil El-Sherif¹, Gioia Turitto²

¹State University of NY, Downstate Medical Center and NY Harbor VA Healthcare System, Brooklyn, NY, USA

²Methodist University Hospital, Brooklyn, NY, USA

Abstract

Electrolyte disorders can alter cardiac ionic currents kinetics and depending on the changes can promote proarrhythmic or antiarrhythmic effects. The present report reviews the mechanisms, electrophysiological (EP), electrocardiographic (ECG), and clinical consequences of electrolyte disorders. Potassium (K⁺) is the most abundant intracellular cation and hypokalemia is the most common electrolyte abnormality encountered in clinical practice. The most significant ECG manifestation of hypokalemia is a prominent U wave. Several cardiac and non cardiac drugs are known to suppress the HERG K⁺ channel and hence the I_K and especially in the presence of hypokalemia, can result in prolonged action potential duration and QT interval, QTU alternans, early afterdepolarizations, and torsade de pointes ventricular tachyarrhythmia (TdP VT). Hyperkalemia affects up to 8% of hospitalized patients mainly in the setting of compromised renal function. The ECG manifestation of hyperkalemia depends on serum K⁺ level. At 5.5–7.0 mmol/L K⁺, tall peaked, narrow-based T waves are seen. At > 10.0 mmol/L K⁺, sinus arrest, marked intraventricular conduction delay, ventricular tachycardia, and ventricular fibrillation can develop. Isolated abnormalities of extracellular calcium (Ca⁺⁺) produce clinically significant EP effects only when they are extreme in either direction. Hypocalcemia, frequently seen in the setting of chronic renal insufficiency, results in prolonged ST segment and QT interval while hypercalcemia, usually seen with hyperparathyroidism, results in shortening of both intervals. Although magnesium is the second most abundant intracellular cation, the significance of magnesium disorders are controversial partly because of the frequent association of other electrolyte abnormalities. However, IV magnesium by blocking the L-type Ca⁺⁺ current can successfully terminate TdP VT without affecting the prolonged QT interval. Finally, despite the frequency of sodium abnormalities, particularly hyponatremia, its EP effects are rarely clinically significant. (Cardiol J 2011; 18, 3: 233–245)

Key words: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, magnesium, sodium, lithium

Introduction

Cardiac arrhythmias are an expression of the same fundamental electrophysiological (EP) principles that underlie the normal electrical behavior of the heart. The electrical activity of the heart depends on transmembrane ionic gradients and the time- and voltage-dependent alterations of their conductance.

The resting membrane potential (V_m) is calculated by the Goldman constant field equation [1],

$$V_m = \frac{RT}{zF} \ln \frac{P_k a_{K_o} + P_{Na} a_{Na_o} + P_{Cl} a_{Cl_i}}{P_k a_{K_i} + P_{Na} a_{Na_i} + P_{Cl} a_{Cl_o}}$$

which incorporates the permeability (P) and activity (a) of all ionic species that contribute to it.

Address for correspondence: Nabil El-Sherif, MD, Cardiology Division, NY Harbor VA Healthcare System, 800 Poly Place, Brooklyn, NY 11209, USA, tel: 718 630 3740, fax: 717 630 3740, e-mail: nelsherif@aol.com

Electrolyte abnormalities may generate or facilitate clinical arrhythmias, even in the setting of normal cardiac tissue. Furthermore, electrolyte aberrations are more likely to interact with abnormal myocardial tissue to generate their own cadre of cardiac arrhythmias. Electrolyte disorders exert their actions by modulating the conduction of ions across specific cardiac membrane channels; and this in turn can result in antiarrhythmic or proarrhythmic sequelae.

Potassium

Potassium is the most abundant intracellular cation and the most important determinant of the resting membrane potential (RMP). The EP effects of potassium depend not only on its extracellular concentration, but also on the direction (hypokalemia *vs* hyperkalemia) and rate of change. Hoffman and Suckling [2] have noted that the effect of potassium on the RMP is modulated by the simultaneous calcium concentration. The interrelationship is such that an elevated calcium level decreases the depolarizing effect of an elevated potassium level, and low calcium levels diminish the depolarization produced by hypokalemia. When extracellular potassium levels are higher than normal, the cell membrane behaves as a potassium electrode, as described by the Nernst equation:

$$V_m = -61.5 \log [K^+]_i/[K^+]_o.$$

At levels of less than ~3 mmol/L, the transmembrane potential (V_m) is less than that predicted by the Nernst equation [3], because hypokalemia reduces membrane permeability to potassium (P_k).

Indeed, potassium currents are modulated by the potassium gradient itself and other electrolytes as well (Table 1) [4]. The conductance of the inward rectifier current (I_{K1}) is proportional to the square root of the extracellular K concentration $[K^+]_o$ [5, 6]. The dependence of the activation of the delayed rectifier current (I_{Kr}) on the extracellular potassium concentration $[K^+]_o$ helps explain why the action potential duration (APD) is shorter at higher $[K^+]_o$ and longer at low $[K^+]_o$ concentrations (Table 1) [7]. As important as the time factor may be on the EP impact of different potassium levels, it is equally important to note that rapid fluctuations in extracellular potassium levels do occur, especially through transcellular shifts (Table 2). Insulin, β -adrenergic agonists, aldosterone, and changes in blood pH may independently affect serum potassium levels [8].

Table 1. Modulation of potassium currents by electrolyte concentration.

I_{K1} , inward rectifier	Its conductance is proportional to the square root of $[K^+]_o$. The instantaneous inward rectification on depolarization is due to the Mg^{2+} block at physiologic $[Mg^{2+}]_i$ [4]
I_{Kr} , delayed rectifier	Low $[K^+]_o$ decreases the delayed rectifier current (I_{Kr})
I_{to} , transient outward	One type is voltage activated and modulated by neurotransmitters The other type is activated by intracellular Ca
$I_{K(Ca)}$	Opens in the presence of high levels of intracellular calcium
$I_{K(Na)}$	Opens in the presence of high levels of intracellular sodium

Table 2. Factors that affect the transcellular shift of potassium.

From inside to outside	From outside to inside
Acidosis	Alkalosis
α -adrenergic receptor stimulation	β_2 -adrenergic receptor stimulation
Digitalis	Insulin
Solvent drag	

Hypokalemia

Hypokalemia is the most common electrolyte abnormality encountered in clinical practice. Potassium values of less than 3.6 mmol/L are seen in over 20% of hospitalized patients [9]. As many as 10% to 40% of patients on thiazide diuretics [10] and almost 50% of patients resuscitated from out-of-hospital ventricular fibrillation [11] have low potassium levels. Hypokalemia results from decreased potassium intake, transcellular shift, and, most commonly, increased renal or extrarenal losses (Table 3).

Electrophysiological effects of hypokalemia

Hypokalemia leads to a higher (more negative) RMP and, at least during electrical diastole, a decrease in membrane excitability as a result of widening of the RMP and the threshold potential (TP) difference. Low extracellular potassium decreases the delayed rectifier current (I_{Kr}), resulting in an increase in the APD and a delay in repolarization.

Table 3. Causes of hypokalemia.

Decreased intake	
Potassium shift into the cell (see Table 2)	
Renal potassium loss	
Increased mineralocorticoid effects	Increased flow to distal nephron
Primary or secondary aldosteronism	Diuretics
Ectopic ACTH-producing tumor or Cushing's syndrome	Salt-losing nephropathy
Bartter's syndrome	Hypomagnesemia
Licorice	Nonresorbable anion
Renovascular or malignant hypertension	Carbenicillin, penicillin
Congenital abnormality of steroid metabolism	Renal tubular acidosis (type I or II)
Renin-producing tumor	Congenital defect of distal nephron
	Liddle's syndrome
Extrarenal potassium loss	
Vomiting, diarrhea, laxative abuse	
Villous adenoma, Zollinger-Ellison syndrome	

It has been suggested that extracellular K⁺ ions are required to open the delayed rectifier channel [7].

Most importantly, hypokalemia alters the configuration of the action potential (AP), with the duration of phase 2 first increasing and subsequently decreasing, whereas the slope of phase 3 decelerates. The latter effect leads to an AP with a long "tail", resulting in an increase in the relative refractory period (RRP) and a decrease in the difference of the resting membrane potential from the threshold potential during the terminal phase of the AP. Thus, cardiac tissue demonstrates increased excitability with associated ectopy for a considerable portion of the AP. Conduction slows because depolarization begins in incompletely repolarized fibers. Furthermore, hypokalemia prolongs the plateau in the Purkinje fibers but shortens it in the ventricular fibers [12]. The AP tail of the conducting system prolongs more than that of the ventricles, increasing the dispersion of repolarization. Hypokalemia increases diastolic depolarization in Purkinje fibers, thereby increasing automaticity.

In summary, the EP effects of hypokalemia are: (1) a decrease in conduction velocity; (2) shortening of the effective refractory period (ERP); (3) prolongation of the RRP; (4) increased automaticity; and (5) early afterdepolarizations (EADs) (Table 4).

Electrocardiographic manifestations of hypokalemia

The electrocardiographic manifestations of hypokalemia [13, 14] can be conceptualized as those due to its effects on repolarization and those emanating from its effects on conduction (Table 5).

Table 4. Electrophysiological effects of hypokalemia.

Decrease in conduction velocity
Shortening of the effective refractory period
Prolongation of the relative refractory period
Increased automaticity
Early afterdepolarizations

Table 5. ECG manifestations of hypokalemia.

Repolarization changes
Decreased amplitude and broadening of the T waves
Prominent U waves
ST segment depression
T and U waves fusion (in severe hypokalemia)
Conduction abnormalities
Increase in QRS duration
Atrioventricular block
Cardiac arrest
Increase in P wave amplitude and duration
Slight prolongation of the P-R interval

The electrocardiographic (ECG) changes resulting from its effects on repolarization include: decreased amplitude and broadening of the T waves; prominent U waves; ST segment depression; and T and U wave fusion, which is seen in severe hypokalemia (Fig. 1). When the U wave exceeds the T wave in amplitude, the serum potassium is < 3 mmol/L. ECG changes due to conduction abnormalities are seen in more advanced stages of hypokalemia and

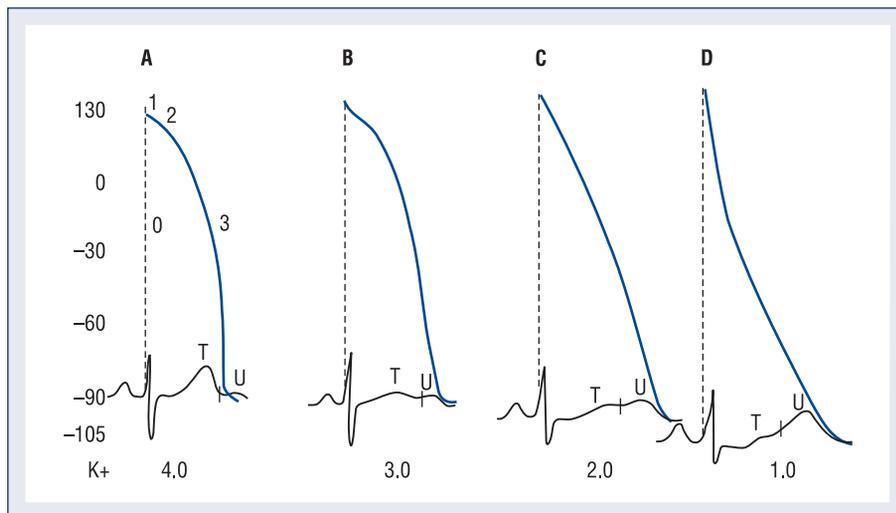


Figure 1. Diagram of the ventricular action potential superimposed on the ECG at different extracellular potassium concentrations (4.0, 3.0, 2.0 mEq/L). The numbers on the left designate the transmembrane potential in millivolts. From [14].

include: increase in QRS duration without a concomitant change in the QRS configuration; atrio-ventricular block (AV); cardiac arrest; increase in P wave amplitude and duration; and slight prolongation of the P–R interval.

Arrhythmogenic potential and clinical implications of hypokalemia

Hypokalemia-induced hyperexcitability is clinically manifested by an increase in supraventricular and ventricular ectopy. In the Framingham Offspring Study, potassium and magnesium levels were inversely related to the occurrence of complex or frequent ventricular premature complexes after adjustment for covariates [15].

Hypokalemia facilitates reentry by slowing conduction during the prolonged RRP and by causing an increase in the dispersion of refractoriness. Its suppressant effect on the Na-K pump leads to intracellular Ca^{2+} overload and this facilitates the development of delayed afterdepolarizations via a transient inward current (I_{ti}). Hypokalemia enhances the propensity for ventricular fibrillation in the normal, as well as the ischemic, canine heart [16]. An association between hypokalemia and ventricular fibrillation in patients with acute myocardial infarction has been well established [17–19].

Several cardiac and non cardiac drugs are known to suppress the HERG K^+ channel and hence the I_{Kr} , and especially in the presence of hypokalemia, result in prolonged action potential duration and QT interval, EADs, and torsade de pointes ventricular tachyarrhythmia (Figs. 2, 3) [20].

Hyperkalemia

Although less common than hypokalemia, hyperkalemia may affect approximately 8% of hospitalized patients in the United States. Hyperkalemia is seen mainly in the setting of compromised renal function, particularly in association with the administration of a variety of nephrotoxic medications. Hyperkalemia may result from either decreased excretion or a shift of potassium from within the cell (Table 6).

Electrophysiological effects of hyperkalemia

The disproportional effects of varying levels of hyperkalemia on the RMP and the TP explain the initial increase in excitability and conduction velocity followed by their decrease as the potassium level increases further (Table 7). Mild-to-moderate levels of hyperkalemia decrease the RMP (less negative) more than the TP, thereby diminishing the difference between the two and increasing excitability. The decrease in the slope of the upstroke of the AP ($\delta V/\delta T$), one of the major determinants of conduction velocity, is counterbalanced by a decrease in the RMP to TP difference, resulting in an ultimate increase in conduction velocity [21]. Severe hyperkalemia is associated with an increase in the difference between the RMP and the TP, leading to a decrease in excitability. Further decrement in the AP upstroke ($\delta V/\delta T$) overwhelms the positive effect of the TP decrease on the conduction velocity, resulting in a definitive decrease of the latter.

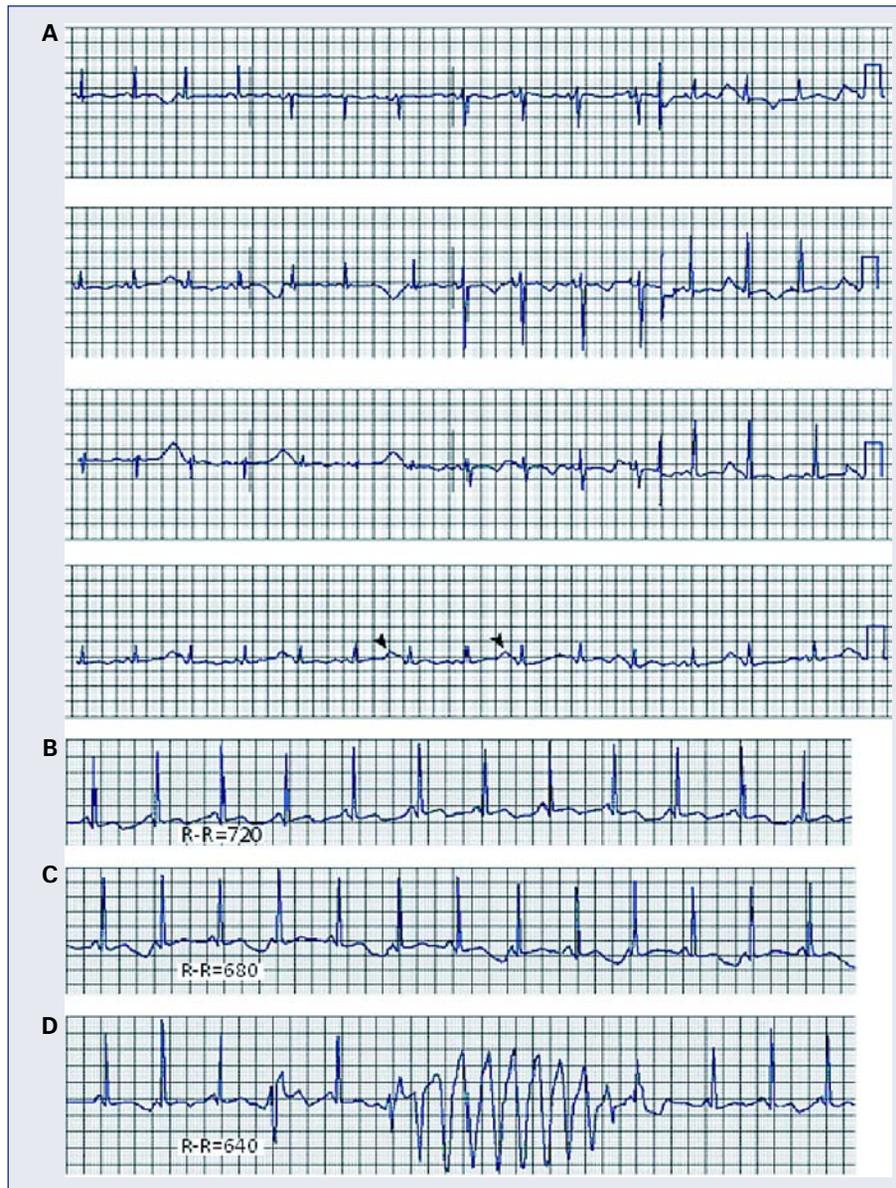


Figure 2. A. Twelve-lead ECG from a patient with hypokalemia and hypomagnesemia showing marked QTU prolongation and QTU alternans (marked by arrowheads); B–D. Representative rhythm strips from the same patient as in A, showing tachycardia-dependent QTU alternans and torsades de pointes [16].

Hyperkalemia is associated with increased membrane permeability to potassium, a consequence of an increase of the inward going rectifier [I_{k1}] and the delayed rectifier current (I_{Kr}) [5–7]. This accelerates the rate of repolarization and shortens the AP duration. Hyperkalemia preferentially shortens the plateau of the Purkinje fibers, thereby decreasing the dispersion of repolarization in the ventricle [12]. Furthermore, it slows the diastolic depolarization of the Purkinje fibers.

The effects of hyperkalemia depend on the tissue involved, with the atrial myocardium being the

most sensitive, the ventricular myocardium less sensitive, and the specialized tissue (sinoatrial node and His bundle) the least sensitive. In other words, the depression of excitability and conduction in the atrium occur at lower extracellular potassium levels than in other types of myocardial tissue, as exemplified by the occasional pacemaker case of atrial noncapture and ventricular capture [22]. The sympathetic nervous system seems to contribute to the sinus node resistance to hyperkalemia [23].

Many investigators have observed regional differences in repolarization time in the nonischemic

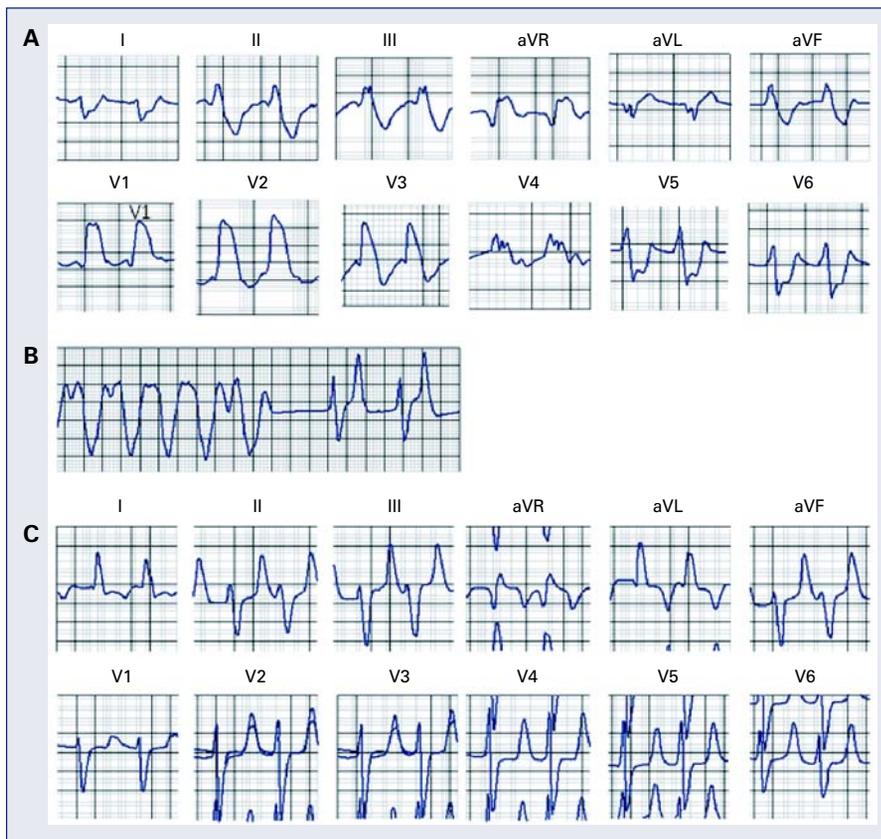


Figure 3. A, B, and C are tracings from a 39 year-old patient with end stage renal disease on dialysis who presented with weakness and palpitations. Chemistry showed a serum potassium level of 10 mEq/L; A. Atypical bundle branch block; the QRS is wide and is merging with the T wave; B. Ventricular tachycardia that failed to respond to adenosine and procainamide given by paramedics; C. Resolution of above ECG changes with dialysis and normalization of serum potassium level.

Table 6. Causes of hyperkalemia.

Decreased excretion
Renal failure
Renal secretory defects
Hyporeninemic hypoaldosteronism
Heparin
Drugs (ACE inhibitors, spironolactone, triamterene, NSAIDs, trimethoprim)
Shift of potassium from within the cell (see Table 2)
Massive release of intracellular potassium
Hypertonicity
Insulin deficiency
Hyperkalemic periodic paralysis

myocardium in response to hyperkalemia. Sutton and colleagues have recorded monophasic action potentials from the endocardium and epicardium in

Table 7. Effect of $[K^+]_o$ on RMP, TP, and V_{max} in ventricular muscle fibers of guinea pigs. From [21].

$[K^+]_o$ [mM]	RMP [mV]	TP [mV]	RMP-TP [mV]	V_{max} [V/s]
2.0	99.4	72.7	26.7	236
5.4	83.0	65.1	17.9	219
10.0	65.8	51.4	14.4	178
11.5	62.8	45.6	17.2	154
13.0	60.7	41.9	18.8	103
16.2	55.4	34.7	20.7	45

RMP — resting membrane potential; TP — threshold potential; $[K^+]_o$ — extracellular potassium concentration

open-chest dogs during graded intravenous infusion of potassium to a plasma level of 9 mmol/L. Their results suggest that the regional differences in repolarization times are mainly a result of local changes in activation times rather than a direct effect on the APD [24].

Table 8. ECG manifestations of hyperkalemia.

Mild hyperkalemia (K = 5.5–7.5 mEq)
Tall, peaked, narrow-based T waves
Fascicular blocks (LAFB, LPFB)
Moderate hyperkalemia (K = 7.5–10.0 mEq)
First-degree atrioventricular block
Decreased P wave amplitude followed by disappearance of the P waves and sinus arrest
ST segment depression
Severe hyperkalemia (K > 10.0 mEq)
Atypical bundle branch block (LBBB, RBBB), IVCD
Ventricular tachycardia, ventricular fibrillation, idioventricular rhythm

LAFB — left anterior fascicular block; LPFB — left posterior fascicular block; LBBB — left bundle branch block; RBBB — right bundle branch block; IVCD — intraventricular conduction delay

An interesting phenomenon, the Zwaardemaker-Libbrecht effect, is the result of a change from a low to high extracellular potassium level and manifests itself by a transient arrest of pacemaker cells, abbreviation of APD, and hyperpolarization [25–27]. This phenomenon underscores the fact that the rate of intravenous administration of potassium is more important — from a proarrhythmic standpoint — than the absolute amount of potassium administered and the final level of extracellular potassium.

Electrocardiographic manifestations of hyperkalemia

The ECG is not a sensitive indicator of hyperkalemia; 50% of patients with potassium levels greater than 6.5 mEq/L will not manifest any ECG changes (Table 8) [14]. The ECG changes due to mild potassium elevations (K = 5.5–7.0 mmol/L) include tall, peaked, narrow-based T waves and fascicular blocks. Moderate hyperkalemia (K = 7.5–10.0 mmol/L) is associated with first-degree AV block and diminished P wave amplitude. As the potassium level increases further, the P wave disappears, and sinus arrest, as well as ST segment depression, may develop. Atypical bundle branch blocks (LBBB and RBBB), intraventricular conduction delays, ventricular tachycardia (Fig. 3), ventricular fibrillation, and idioventricular rhythm are more commonly seen in cases of severe hyperkalemia (K⁺ > 10.0 mmol/L). The bundle branch blocks associated with hyperkalemia are atypical in the sense that they involve the initial and terminal forces of the QRS complex. Shifts in the QRS axis indicate disproportionate conduction delays in the left

bundle fascicles. These manifestations of intraventricular conduction delay correlate with a prolonged intracardiac H–V interval [28]. As hyperkalemia progresses, depolarization merges with repolarization, expressed in the ECG with QT shortening and apparent ST segment elevation simulating acute injury. The latter disappears with hemodialysis — dialyzable current of injury [29]. The effect of hyperkalemia on QRS morphology of ventricular paced beats have also been studied [30]. Hyperkalemia is the most common electrolyte abnormality to cause loss of capture. In patients with pacemakers, hyperkalemia causes two important clinical abnormalities: (1) widening of the paced QRS complex (and paced P wave) on the basis of delayed myocardial conduction; when the K level exceeds 7 mEq/L, the intraventricular conduction velocity is usually decreased and the paced QRS complex widens (Fig. 4); (2) increased atrial and ventricular pacing thresholds with or without increased latency [30].

The parallel changes in the AP and ECG can be appreciated better by reviewing Figure 5 [14].

Arrhythmogenic potential and clinical implications of hyperkalemia

Potassium and myocardial ischemia. In the early phases of an ischemic insult, the cardiac membrane becomes increasingly permeable to potassium. After coronary ligation in pigs [31, 32], the rise in extracellular potassium concentration results in currents of injury, refractory period shortening, conduction slowing, and ventricular fibrillation. During ischemia, APD shortening is more pronounced and the conduction velocity is slower in failing than in control myocardium. Extracellular potassium [K⁺]_o reaches higher values during acute ischemia in failing *vs* normal myocardium. Increased spatial dispersion in EP parameters and [K⁺]_o over the ischemic border in failing hearts may explain the higher propensity for reentrant arrhythmias during acute regional ischemia [33].

Potassium and calcium abnormalities. The combination of hyperkalemia and hypocalcemia has a cumulative effect on the atrioventricular and intraventricular conduction delay and facilitates the development of ventricular fibrillation. Hypercalcemia, through its membrane-stabilizing effect, counteracts the effects of hyperkalemia on AV and intraventricular conduction and averts the development of ventricular fibrillation. This protective effect of calcium is immediate and its intravenous administration should be the first therapeutic measure in cases of hyperkalemia.

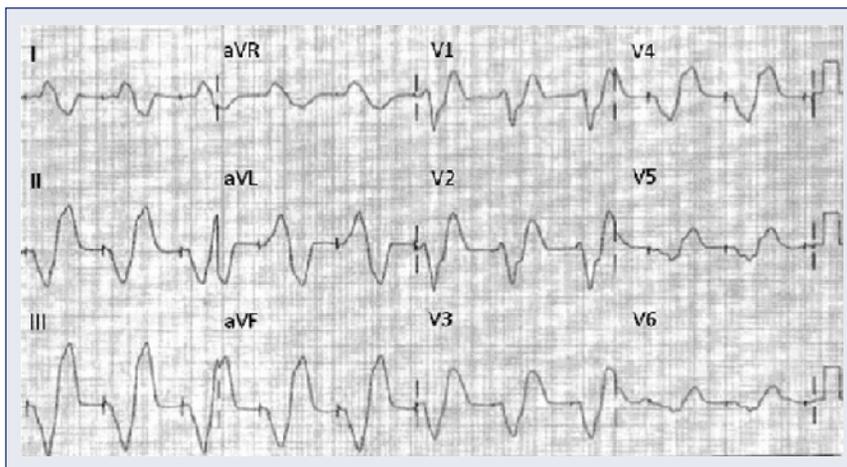


Figure 4. This 12-lead ECG is from a 74 year-old patient with a history of pacemaker implantation for sick sinus syndrome, who presented to the Emergency Room with complaints of “weakness”. He went into asystole shortly afterwards. His potassium serum level at the time of the cardiac arrest was 10 mEq/L.

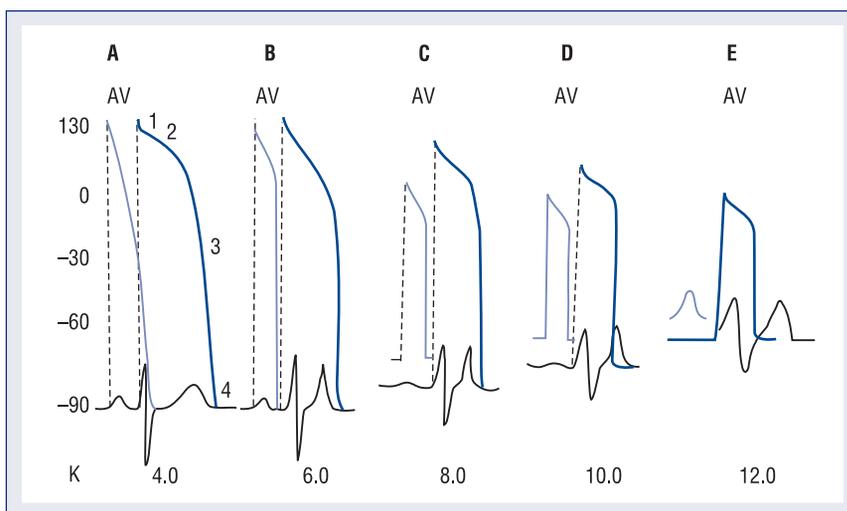


Figure 5. Diagram of an atrial and ventricular action potential superimposed on the ECG for extracellular potassium at 4.0, 6.0, 8.0, 10.0, and 12.0 mEq/L. The numbers on the left designate the transmembrane potential in millivolts, and the numbers at the bottom designate extra cellular potassium concentration [mEq/L]. From [14].

Potassium and digitalis. Hyperkalemia inhibits glycoside binding to (Na⁺, K⁺) ATPase, decreases the inotropic effect of digitalis, and suppresses digitalis-induced ectopic rhythms. Alternatively, hypokalemia increases glycoside binding to (Na⁺, K⁺) ATPase, decreases the rate of digoxin elimination, and potentiates the toxic effects of digitalis.

Calcium. Isolated abnormalities of calcium concentration produce clinically significant EP effects only when they are extreme in either direction. As expected by reviewing the Goldman equation, extra-

cellular calcium concentrations in the physiologic range have no appreciable effect on the resting membrane potential. Hypocalcemia and hypercalcemia have opposing effects on the APD and ERP by affecting intracellular calcium concentration and modulating potassium currents [2].

Hypocalcemia

Hypocalcemia is most frequently seen in the setting of chronic renal insufficiency and is usually associated with other electrolyte abnormalities.

Generally, hypocalcemia may result from decreased intake or absorption or an increase in calcium loss (Table 9).

Electrophysiological effects of hypocalcemia

Low extracellular calcium decreases the slow inward current and intracellular calcium concentration during the AP plateau. The latter decreases outward current, possibly via $I_{K(Ca)}$, prolonging phase 2 of the AP, the total APD, and the duration of the ERP. As a consequence of low intracellular calcium, contractility decreases. Moreover, hypocalcemia slightly decreases the rate of diastolic depolarization in the Purkinje fibers and increases excitability through a direct interaction with the sarcolemma.

Electrocardiographic manifestations of hypocalcemia

The ECG changes of hypocalcemia involve a prolongation of the ST segment and QTc interval and T wave alterations, including upright, low, flat, or sharply inverted T waves in leads with an upright QRS complex (Fig. 6).

Hypercalcemia

Hypercalcemia occurs most commonly in the setting of hyperparathyroidism or as a consequence of several malignancies. A plethora of other causes account for the remaining clinically encountered cases (Table 10).

Table 9. Causes of hypocalcemia.

Decreased intake or absorption
Malabsorption
Decreased absorptive area (small bowel bypass, short bowel)
Vitamin D deficit (decreased absorption, decreased 25-hydroxy-D or 1,25-dihydroxy-D production)
Increased loss
Alcoholism
Chronic renal insufficiency
Diuretic therapy (furosemide, bumetanide)
Endocrine disease
Hypoparathyroidism or pseudohypoparathyroidism
Medullary carcinoma of the thyroid (calcitonin secretion)
Familial hypocalcemia
Physiological causes
Associated with decreased serum albumin (normal calcium ion concentration)
Decreased end-organ response to vitamin D
Sepsis, hyperphosphatemia, induced by aminoglycoside antibiotics, plicamycin, loop diuretics, foscarnet

Electrophysiological effects and electrocardiographic manifestations of hypercalcemia

High extracellular calcium levels shorten the AP plateau, the total APD, and, consequently, the

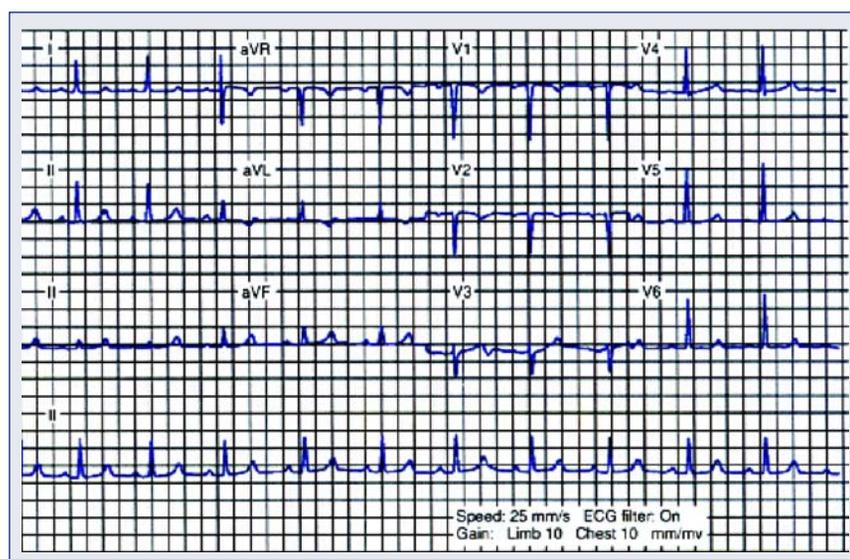


Figure 6. This 12-lead ECG is from a 24 year-old black female patient with sickle cell disease, end stage renal disease, and hyperparathyroidism. The patient’s serum calcium level was 7 mg/dL and the potassium level was 6.5 mEq/L. This ECG demonstrates a prolongation of the ST segment and QTc interval (leads V5 and V6).

Table 10. Causes of hypercalcemia.

Increased intake or absorption
Vitamin D or vitamin A excess
Endocrine disorders
Primary hyperparathyroidism or secondary hyperparathyroidism (renal insufficiency, malabsorption)
Acromegaly
Adrenal insufficiency
Neoplastic diseases
Tumors producing PTH-related protein (ovary, kidney, lung)
Multiple myeloma (osteoclast-activating factor)
Miscellaneous causes
Thiazides
Sarcoidosis
Paget's disease of the bone
Hypophosphatasia
Familial hypocalciuric hypercalcemia
Idiopathic

duration of the ERP. A study of the effect of hypercalcemia on the guinea pig ventricular AP suggested that a decrease in the inward $\text{Na}^+/\text{Ca}^{++}$ exchange current might be largely responsible for the shortening of the AP [34]. Elevated extracellular Ca^{2+} concentration has a stabilizing effect on the membrane, increasing the extent of depolarization needed to initiate an AP. In addition, hypercalcemia has a positive inotropic effect, decreases excitability [35], and slightly increases the rate of diastolic depolarization in the Purkinje fibers. The ECG changes as a result of hypercalcemia are limited to shortening or elimination of the ST segment and decreased QTc interval.

Magnesium

Magnesium is the second most abundant intracellular cation after potassium. The significance of magnesium disorders has been debated because of difficulties in accurate measurement and their frequent association with other electrolyte abnormalities [36, 37]. It is an important cofactor in several enzymatic reactions contributing to normal cardiovascular physiology. Magnesium deficiency is common, but its EP sequelae have evaded even the closest scrutiny. Magnesium therapy in pharmacologic doses has been beneficial in treating torsades de pointes. Magnesium toxicity rarely occurs except in patients with renal dysfunction.

Electrophysiological effects and electrocardiographic manifestations of hypomagnesemia and hypermagnesemia

In the presence of extremely low extracellular calcium concentrations, magnesium exerts an effect on the current or currents that modulate the duration of the ventricular AP plateau. Hoffman and Suckling [2] found that in the presence of normal calcium concentrations, magnesium deficiency had little effect on the AP of the canine papillary muscle. However, when the calcium concentration was lowered to 1/10 of normal, complete omission of magnesium in the superfusate prolonged the AP plateau, which was already increased in duration by low calcium, from a normal value of 100 to 150 ms to 1000 ms or more.

Magnesium blocks the calcium channel, shifts the steady-state inactivation curve of the fast sodium channel in the hyperpolarizing direction, modifies the effect of hyperkalemia, and exerts modulating effects on several potassium currents. Hypermagnesemia depresses AV and intraventricular conduction. DiCarlo et al. [38] observed the following ECG effects of intravenous administration of magnesium in patients with normal baseline serum magnesium and other electrolyte levels: (1) prolongation of sinus node recovery time (SNRT) and corrected SNRT; (2) prolongation of the AV nodal functional, relative, and ERP; (3) a small increase in QRS duration during ventricular pacing at cycle lengths of 250 and 500 ms; and (4) a significant increase in the atrial-His interval and the atrial paced cycle length causing AV node Wenckebach conduction.

Kulick et al. [39] in studying healthier hearts, noted the following ECG effects of intravenous magnesium administration: (1) significant prolongation of the P-R interval from 145 to 155 ms after magnesium infusion; (2) prolongation of the atrial-His interval; (3) prolongation of the sinoatrial conduction time; (4) prolongation of the AV nodal ERP; and (5) no significant increase in SNRT in the atrial paced cycle length causing AV node Wenckebach conduction or in QRS duration. Hypermagnesemia and hypomagnesemia do not produce specific ECG changes.

Magnesium and torsades de pointes

The administration of intravenous magnesium sulfate to patients with prolonged Q-T interval and torsades de pointes, whether the initial magnesium level is normal or low, may suppress ventricular tachycardia. Takanaka et al. [40] studied the effects of

magnesium and lidocaine on the APD and on barium-induced EADs in canine Purkinje fibers. Their data suggest that hypomagnesemia may be arrhythmogenic when combined with hypokalemia and bradycardia, and magnesium administration may suppress triggered activity, mainly by directly preventing the development of triggered APs. In conclusion, magnesium sulfate is a very effective and safe treatment for torsades de pointes [41].

Magnesium and heart failure

In a sample of ambulatory patients with heart failure, magnesium depletion in serum and tissue did not appear to occur more commonly in patients with serious ventricular arrhythmias than in patients without serious ventricular arrhythmias [42]. In patients with moderate to severe heart failure, serum magnesium does not appear to be an independent risk factor for either sudden cardiac death or all-cause mortality [43]. Hypomagnesemia was found to be associated with an increase in frequency of ventricular couplets, but it did not lead to a higher incidence of clinical events [43].

Magnesium and myocardial infarction

Magnesium administration has been found to have a positive effect on the consequences of myocardial infarction in experimental models. Its effect in the clinical setting of myocardial infarction has been controversial. In the LIMIT-2 study, magnesium administration was noted to have a positive effect on mortality rate, a finding that has not been reproduced in the ISIS-4 trial [44–49].

Relationship between potassium, magnesium, and cardiac arrhythmias

No specific EP effects or arrhythmias have been linked to isolated magnesium deficiency. Nonetheless, magnesium may influence the incidence of cardiac arrhythmias through a direct effect, by modulating the effects of potassium, or through its action as a calcium channel blocker. Magnesium deficiency is thought to interfere with the normal functioning of membrane ATPase, and thus the pumping of sodium out of the cell and potassium into the cell. This affects the transmembrane equilibrium of potassium, which may result in changes in the resting membrane potential, changes in potassium conductance across the cell membrane, and disturbances in the repolarization phase [50].

Sodium

Sodium is the most abundant extracellular cation, and the sodium current determines the phase 0 and amplitude of the AP. Its conductance increases precipitously with the initiation of the AP, allowing its transmembrane gradient to determine the first phase of the AP, and, consequently, its ultimate configuration. Hence, hypernatremia increases and hyponatremia decreases phase 0 of the AP by altering the transmembrane sodium gradient. The upstroke of the AP is determined by the sodium gradient and the transmembrane potential. Therefore, hypernatremia, by increasing the sodium gradient, negates many of the effects of hyperkalemia, which decreases the transmembrane potential. By increasing the amplitude of the AP, high sodium levels prolong the APD. In vitro, an increased Na concentration restores the normal configuration of AP that is altered by previous treatment with sodium channel blockers. Despite the frequency of sodium abnormalities, particularly hyponatremia, its EP effects are rarely of clinical significance.

Lithium

Although lithium is not a naturally occurring electrolyte, it is frequently encountered clinically in the treatment of manic-depressive disorders and, as such, its potential adverse effects on the sinoatrial node should not be overlooked. Lithium is associated with sinoatrial node dysfunction (sinus bradycardia, sinoatrial arrest, or exit block, either type I or type II) and reversible T wave changes [51–53].

Acknowledgements

The authors do not report any conflict of interest regarding this work.

This work is supported by Department of Veterans Affairs Medical Research Funds to Nabil El-Sherif, MD.

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