K^+ K^+ K^+ K^+ K^+K^+ K^+ K^+ K^+ K^+K^+ K^+ K^+ K^+ K^+K^+ K^+ K^+ K^+ K^+K^+ K^+ K^+ K^+ K^+

Hyperkalemia

Pharmacy 655- Pharmacotherapy III
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Objectives

- **Summarize the common causes and the clinical presentation of hyperkalemia**
- **Recommend a strategy to avoid drug-induced hyperkalemia**
- **Recommend therapy for hyperkalemia**

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Reading Assignment

- **Review the Potassium Balance and the Sodium/Water Balance material from *Pharmacotherapy II* lectures**
- ***Pharmacotherapy, 9th ed*: pp 783-784, 788-792 (supplemental to lecture material)**

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Potassium Homeostasis

- Normal adult total body K^+ 50-55 mMol/kg; >95% intracellular
- Avg daily turnover 50-150 mMol;
  - excretion 90% renal,
  - 10% GI;
  - aldosterone ↑'s excretion

- ICF/ECF distribution
  - Na/K ATPase in cell membranes
  - Insulin increases intracellular potassium
  - $\beta 2$ adrenergic receptor increases intracellular K^+
  - exchange with H^+ (*variable* effect of pH on K^+)

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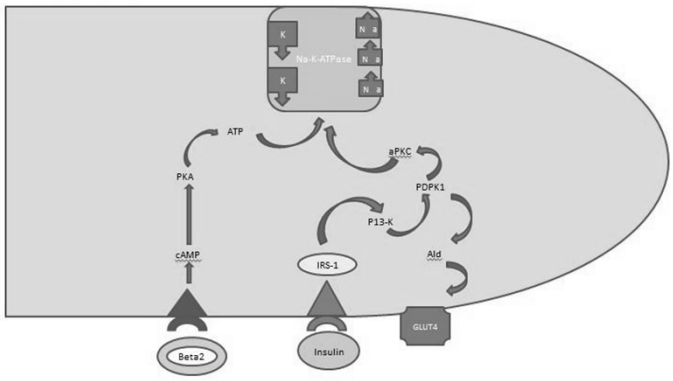
Potassium Homeostasis

- Aldosterone & Insulin secretion are modulated by K level- helps to prevent hyperkalemia
- Serum K^+ normally 3.5-4.8 mMol/L



E-Journal Cardiac Practice 2016;14:11=24

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Pseudohyperkalemia

- Result of collection/preparation of blood specimen
- Fist-clenching during phlebotomy
- Prolonged tourniquet application
- Hemolysis due to traumatic venipuncture
- Delayed processing of sample (esp when on ice)
- Severe leukocytosis (> $100x10^3$/uL) or thrombocytosis (> $1000x\ 10^3$/uL)

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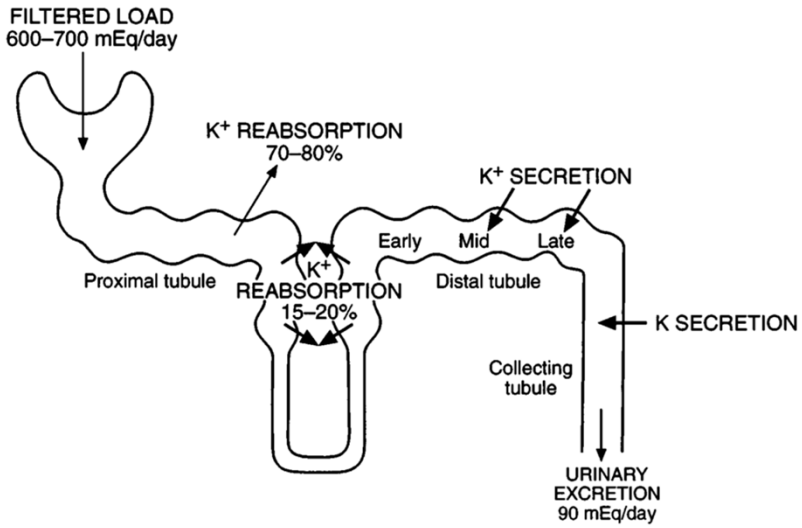
Potassium Handling in Kidney



Only 15% of filtered K is actually excreted

Monthly J Assoc Physicians 1997;90:487-492.

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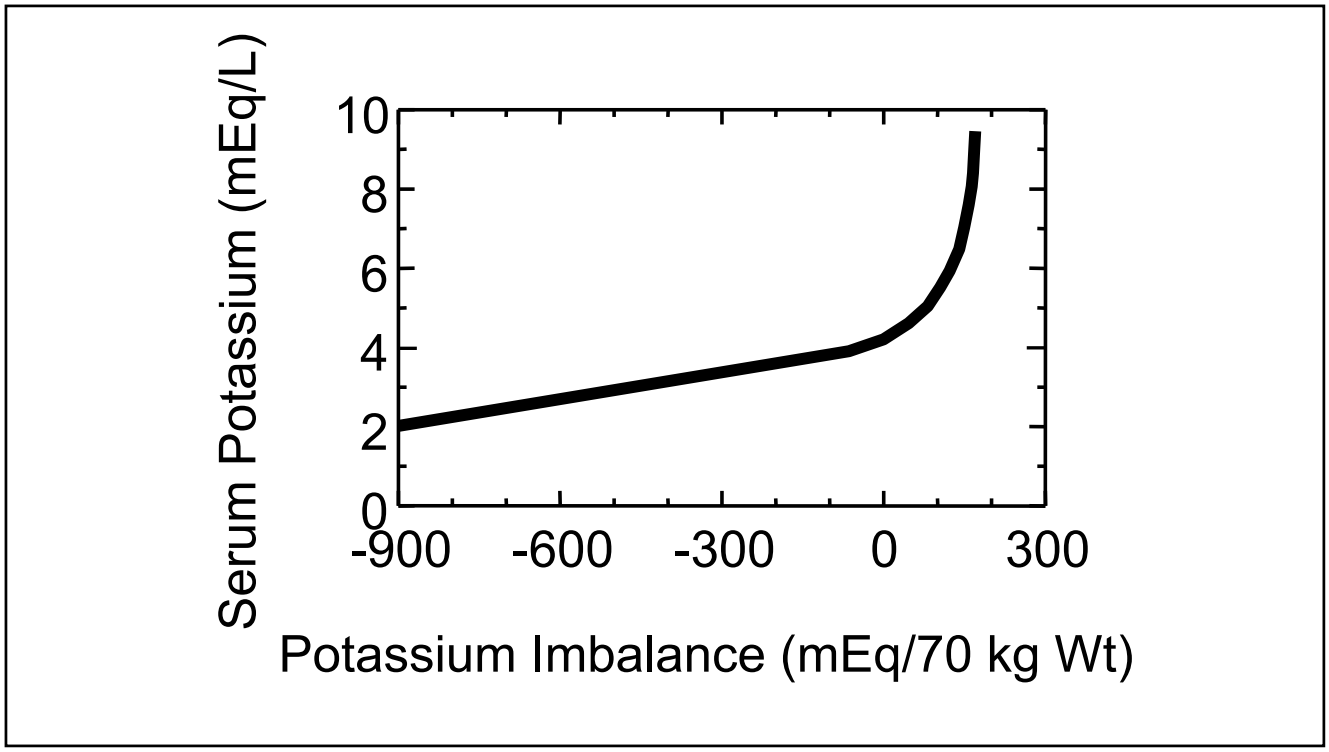
Serum Potassium (mEq/L)
10
8
6
4
2
0
-900
-600
-300
0
300
Potassium Imbalance (mEq/70 kg Wt)

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Hyperkalemia- Causes

- **Renal insufficiency (GFR<30 increases risk)**
- **Decreased Aldosterone**
  - ***ACE inhibitors; A-II receptor blockers (ARBs)*; heparin; adrenal insufficiency**
  - **When kidney and RAAS are normal – normal K is maintained despite wide extremes in intake**
- **Inhibitors of renal secretion of K^+**
  - ***spironolactone/eplerenone* (aldosterone antagonists)**
  - **triamterene, amiloride, trimethoprim**

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Hyperkalemia - Causes

- **ECF/ICF equilibrium**
  - **insulin insufficiency, β_2 blockers, digitalis intoxication, succinylcholine, acidosis**
- **Intake of K > amount that can be excreted**
  - **e.g. *salt substitutes or KCl supplements* in pt. with renal insufficiency or K-sparing diuretic Rx; coconut water**

Hyperkalemia- Clinical Presentation

- **Conduction disturbances on ECG ± skeletal muscle weakness**
  - **may develop at serum K>6.5**
  - **Cardiotoxicity present in ~all cases with serum K>8 mmol/L**
- **ECG changes:**
  - **↑ T-wave appears 1st –not dangerous**
  - **↓ P-wave, ↑ PR, ↑ QRS -should be treated immediately**
  - **potentially lethal dysrhythmias**
- ***"the first symptom of hyperkalemia is death"***

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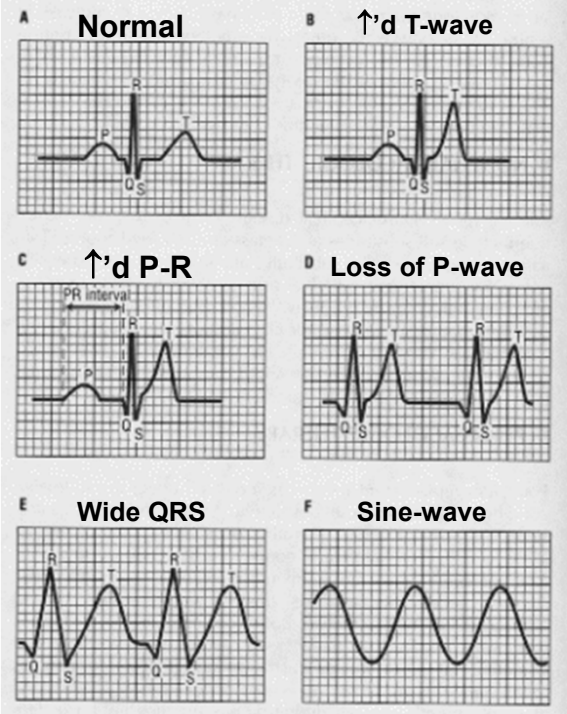
ECG effects of hyperkalemia

(*Pharmacotherapy, 9th ed, p. 789)*



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Increasing Incidence of Drug-Induced Hyperkalemia

Canadian study (NEJM 2004; 351:543):

- >7-fold increase in Rx's for spironolactone from 1998 to 2001 after publication of RALES CHF trial
- mostly in elderly CHF pts who also were on ACE inhibitors, many also had ↓'d renal fcn
- 3-fold increase in hospital admissions for hyperkalemia, and 2-fold increase in deaths associated with hyperkalemia in same time period

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Strategy for Patients at Risk for Drug-Induced Hyperkalemia

- Assess renal function- GFR<30 higher risk
- Diabetes, decompensated CHF, advanced age, multiple drugs that affect K^+ - higher risk
- Reduce K^+ intake- K^+ supplements, salt-substitutes, herbals/supplements (e.g. coconut water, noni juice, alfalfa, dandelion, horsetail, nettle)
- Avoid adding aldosterone antagonist Rx if baseline serum K>5.0 mmol/L

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Strategy for Patients at Risk for Drug-Induced Hyperkalemia

- Limit spironolactone dose to 25mg/d if on ACE-I, and avoid spironolactone if on ACE-I & GFR<30
- Check serum K^+ at 3 and 7days after start Rx or ↑ dose of aldosterone antagonist
  - If K^+ rises, but not >5.5 mMol/L, adjust drugs
  - If K^+ >5.5 mMol/L, discontinue drug

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Therapy for Hyperkalemia

- **Minimize K intake**

1. **Physiological antagonism of membrane actions**
   - **IV *Calcium* if acute ECG disturbances**
2. **Intracellular shift with *Insulin*, β_2*-agonist***
3. **Removal from body with *renal excretion*, *dialysis*, *Na Polystyrene Sulfonate, patiromer; zirconium silicate***

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Therapy for Hyperkalemia

Mechanism	Action
Antagonism of membrane actions	• Intravenous calcium**
Extracellular to Intracellular shift	• Insulin and glucose • Sodium bicarbonate (esp if metabolic acidosis) • Beta-2 adrenergic agonists
K removal from body	• Renal excretion - Loop/thiazide diuretics • K binders • Dialysis (HD if severe)

** Calcium should be combined with therapies that shift K intra-cellularly (not used in monotherapy)

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Calcium Rx for Hyperkalemia

- **IV Calcium antagonizes the membrane effects of hyperkalemia**
- **Used to control cardiotoxicity of hyperkalemia until serum K^+ levels can be reduced**
- **Ca^{++} Rx does *not* affect serum K^+ level**
- **Rapid onset, duration <30 min; may repeat dose**
- **i.v. injection 4.8-9.6 mEq over 3-5 min**
- **Note $CaCl_2$ = 13.6 mEq/g; CaGluconate = 4.8 mEq/g**

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Calcium Rx for Hyperkalemia

Which calcium salt should we use?

- **Equimolar doses of calcium are therapeutically equivalent**
- **Calcium gluconate less irritating to vein, so often the preferred choice**
- **Calcium chloride available in prefilled syringes- often used for emergency drug supplies**

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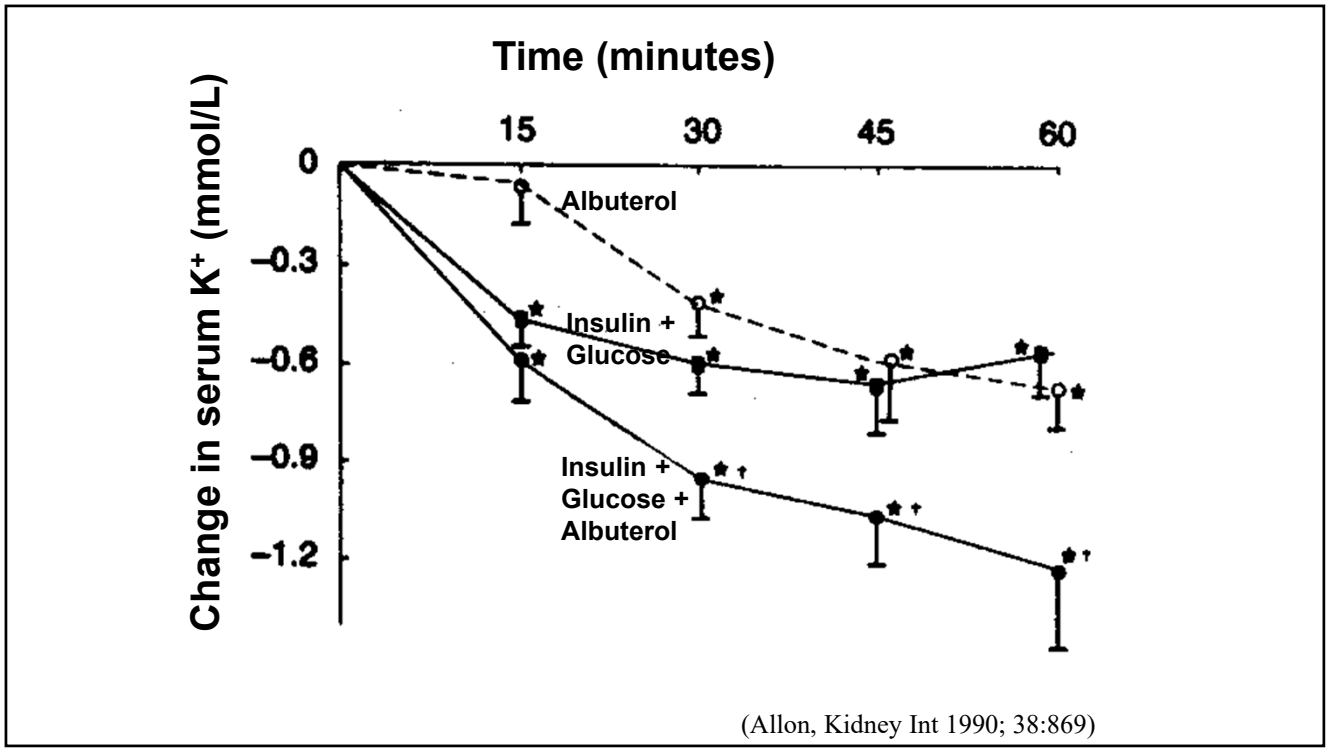
Intracellular K^+ Shift for Hyperkalemia

- **Insulin**
  - IV push 10-20 units regular insulin + 25 g 50% dextrose (glucose)
  - or IV infusion of 500-1000 ml 10% dextrose with insulin 20u over 1 hr
  - if blood glucose is elevated, inject insulin without dextrose
  - onset <15 min, duration several hrs
- **$Beta_2$ agonist**
  - albuterol 20 mg per nebulizer
  - or terbutaline 7 mcg/kg s.c. injection
  - onset <30 min; duration about 2 h
  - works best as combination with insulin Rx
  - Caution in patient with heart disease
- **Na Bicarbonate-** variable response; use only if patient has metabolic acidosis in addition to hyperkalemia



(Allon, Kidney Int 1990; 38:869)

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Potassium Removal

- **Renal Excretion**
  - **if renal fcn is ok; ± thiazide or loop diuretic**
- **Dialysis**
  - **hemodialysis rapidly lowers serum K+**
- **Na Polystyrene Sulfonate (Kayexalate®; SPS)**
  - **Na/K exchange in gut**
  - **maximum 0.3-1.0 mEq K+ exchanged per g resin**
  - **given 15-30 g p.o. or 50 g as retention enema**
  - **sorbitol 33% added in suspension dosage forms to prevent constipation**
  - **Small risk of serious intestinal mucosal injury; FDA recommends not using with sorbitol; most reports associated with 70% sorbitol + SPS**
  - **Onset about 2 hr; maximal effect within 6 hrs; repeat doses if needed q 4-6 hrs.**
  - **Old drug without any definitive studies that demonstrate efficacy- questions of potential benefit vs potential risk**

New Oral K-Binder Drugs

- **Patiromer (Veltassa®)**
  - FDA-approved for Rx of mild-moderate hyperkalemia
  - Black-box warning to avoid taking with other oral medications within 6 hrs
  - Powder packets to suspend in water, dosed once daily;
    - start 8.4 g & increase q week if necessary to max 25.2 g; 30 packets cost ~$600
  - May allow CHF and CKD pts to continue RAAS inhibitors or spironolactone Rx
  - Side effects:
    - **Constipation**
    - **Hypomagnesemia**
  - **Drug interactions:**
    - **Decreases serum concentration of: ciprofloxacin, levothyroxine, metformin**

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New Oral K-Binder Drugs

- **Sodium Zirconium cyclosilicate (Lokelma®)**
  - **Powder packets for oral suspension**
  - **Recommended 10g TID x 48 hours, then:**
    - **10g once daily, then titrate weekly**
  - **CONTAINS 400 mg sodium per 5g!!**
    - **This is a concern in patients with HF and CKD**
  - **Unlikely to cause hypomagnesemia**
  - **Fewer medication interactions – can be taken with other medications**
  - **Side Effects:**
    - **Edema (more common with doses 15g/day)**
    - **Constipation**
  - **Drug Interactions**
    - **Increases exposure to warfarin**
    - **Decreases exposure to clopidogrel and dabigatran**

Potassium Binders

- ***Neither*** **of these drugs has been studied in the context of acute Rx of severe hyperkalemia**

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Summary- Hyperkalemia

- **Causes-**
  - **note importance of renal function & drug Rx**
  - **intake vs excretion; 150 mEq total body excess may be severe**
- **Presentation-**

  -cardiotoxicity & muscle weakness
- **Treatment-**
  - **Antagonize cardiotoxicity (i.v. calcium)**
  - **Shift K^+ into cells (insulin, $\beta 2$ agonist)**
  - **Remove K^+ (kidneys, dialysis, K-binder agents)**
  - **Multiple Rx for overlapping time courses & increased efficacy**

Intravenous Admixtures of Hyperkalemia

Agent	Solution	Administration
Calcium Gluconate	1000 mg (10 mL of a 10% solution)	Over 2-3 min
Calcium carbonate	500-1000 mg (5-10mL of a 10% solution)	Over 2-3 min
Insulin	10-20 units in 500 mL of 10% dextrose OR 10 unit bolus, then 50 mL of 50% dextrose (25 g glucose)	Over 60 min
Furosemide	40 mg IV BID (if hypervolemic with good renal function) 40 mg IV BID with isotonic saline to correct volume if euvolemic or hypovolemic	

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