Pathophysiology
Potassium Balance

I. Electrolyte composition of the Extracellular and Intracellular compartments (Slide 1)
   A. Main extracellular (EC) cation is sodium
   B. Some potassium, calcium, and magnesium and attendant anions in EC fluid
   C. Main intracellular (IC) is potassium with the concentration being around 140 mEq/L
   D. The IC anions are organic, i.e. phosphate, protein, etc.
   E. The average muscle cell has 140 mEq/L (slide says 125) x total body water = total potassium content
      1. An average 70 kg man has 60% water or 42 L of water. 2/3 (28 L) is IC, 1/3 (14 L) is EC.
      2. Therefore 28 L x 140 (or 125) gives you between 3-4,000 mEq of potassium in the IC space
      3. In EC compartment, there is only 4 mEq/L. 14 L x 4 = 56mEq of potassium in the EC space
      4. More than 98% of total body potassium is IC, therefore serum potassium doesn't really say much about total body potassium (serum potassium can be high, low, or normal associated with high, low or normal total body potassium)
   F. Intake of potassium is 100mEq. This is mostly eliminated in urine (92 mEq in urine and 8 mEq in stool)
      1. In cases of diarrhea, patient can lose more potassium in stool, which can affect total body potassium

II. Body's handling of potassium
   A. Sodium excretion
      1. Body sodium concentration is 140 mEq/L.
      2. The body filters 180 L/day therefore 25,000 mEq of sodium is filtered daily.
      3. The body reabsorbs all except 150 mEq, which is eliminated in the urine.
   B. Potassium excretion
      1. Different from sodium because it is tied to hydrogen ion excretion and other processes.
      2. About 750 mEq of potassium/day (4 mEq/L x 180 L/day) are filtered
      3. The body reabsorbs all of the filtered potassium and excretes extra potassium that needs to be eliminated
   C. Micropuncture study done on rats
      1. In figure, there are sections on activity in proximal and distal tubules and the last section is the final urine

2. Micropuncture done at various parts along the tubule and creatinine and potassium are measured (creatinine measured to monitor water reabsorption, which explains changes in potassium concentration changes, i.e. excretion or secretion)
3. Along proximal tubule potassium concentration decreases which signifies reabsorption
4. In the distal tubule, potassium concentration starts off low but then tends to rise. This signifies secretion.
5. On a low potassium diet (middle figure), secretion is not desired therefore potassium concentration is low on proximal and distal tubules and potassium in urine is low
6. On a high potassium diet (bottom figure), the concentration decreases along proximal tubule and rises significantly in distal tubule.

D. Secretion occurs in principal cells of distal tubule
   1. Principal cells also involved in reabsorption of sodium
   2. Several factors affect renal potassium secretion and sodium absorption—amount of Na+ delivered to area and presence of aldosterone
   3. Channels in apical membrane for Na+ entry and K+ exit
   4. Aldosterone opens Na+ channels, increases the number of Na+ channels, opens K+ channels, and stimulates Na/K ATPase in basolateral membrane (important because it decreases the IC Na+ concentration → facilitates Na+ entry at apical membrane and moves K+ into cell, which increases IC pool of secretable K+)
   5. When Na+ is reabsorbed, an anion (Cl- usually) must also be absorbed otherwise luminal electronegativity forms
      a. When a positive moves, it leaves behind a "negative space"
      b. Unless a negative moves, another positive must take its place
   6. Factors involved in sufficient K+ secretion (Favorable electrochemical gradient slide)
      a. Sodium delivery to area
      b. Sodium reabsorption (creates a sink for K+ and H+)
      c. Mineralocorticoid (aldosterone)
      d. Functioning nephron
      e. Absence of blocking agents (ex. Ameloride block reabsorption of Na+ and secretion of K+)
      f. Impermeant anions like sulfate and bicarb should not be easily absorbed in the area to maintain the luminal electronegativity which attracts K+

III. Factors involved in regulation of K+ balance (Table 7.1 of Rose and Rennke)
   A. Intake of K+

1. Insulin, epinephrine, and plasma potassium concentration all govern potassium uptake by cells
    a. Insulin, and epinephrine stimulate Na/K ATPase in non-renal and renal cells, therefore K+ is taken up and Na+ extruded
    b. The epinephrine effect is a beta-adrenergic effect
    c. Increases in plasma K+ concentration stimulates movement of K+ into the cell

B. Urinary excretion is governed by
1. Aldosterone,
2. Distal flow of Na+ and water
    a. The more Na+ delivered to distal tubule, the more Na+ can be reabsorbed and more K+ can be "exchanged"
3. Plasma potassium concentration
    a. Plasma K+ concentration stimulates K+ secretion in distal tubule

C. Factors involved in moving K+ into or out of the cell because of a small amount of K+ leaks out, there can be a considerable change in K+ concentration

D. Slide illustrating beta-adrenergic blockade on K+ handling (Fig. 7.1 p 173 of Rose and Rennke)
1. Normal subjects given K+ load
2. K+ rises but after approx. 60 minutes, serum K+ falls to baseline showing K+ handled intracellularly (not excreted in urine)
3. If patients given propanolol, a beta blocker, the rise is higher and sustained longer (shows you need beta adrenergic stimulation to handle normal K+ load)

E. Body handles K+ efficiently
1. If you were to increase K+ intake from 100mEq/day to 400mEq/day, in 2 days, the urinary K+ will reflect intake (Fig. 7.3, p 176)
2. As serum K+ concentration increases, aldosterone secretion increases and you maintain K+ balance
3. K+ adaptation occurs
    a. Na/K ATPase is stimulated maximally and over time it no longer need a high level of aldosterone to remain operative
    b. So although aldosterone falls to close to normal, these cells still generated high movement of Na+ out and K+ in, increasing secretory pool so K+ can be secreted normally
    c. Serum K+ concentration also falls because you don't need to maintain high serum K+ or high aldosterone to handle load
4. This means that as long as kidneys are normal, you should maintain normal serum K+

F. A study done on adrenalectomized dogs (Fig 7.4 p 181)

1. Dogs given various doses of aldosterone supplements—an inadequate dose of 20 μg, normal dose of 50 μgm and a high dose of 250 μg per day
2. Animals on low dose went into K+ balance, but the serum K+ was high
3. On the normal dose, K+ is in normal range
4. On high dose, K+ is not elevated because you can secrete more
5. With normal aldosterone, and normal kidneys, one should handle K+ loads

IV. Causes of Hyperkalemia (Table 7.2 pg 178)

A. Increased K+ intake—doesn't play a large factor unless there is a major crush injury which results in muscle breakdown or is associated with shock, decreased cardiac output, or decreased renal blood flow, therefore the kidney can't excrete K+

B. Decreased K+ entry into cells

1. Metabolic acidosis
    a. Moves K+ out of cells
    b. Hydrogen ion is buffered intracellularly. H+ moves into cell and a positive ion has to leave (unless a negative ion moved in) therefore K+, the main IC cation, leaves
    c. An organic acidosis will not result in increased K+ concentration
2. Insulin deficiency
    a. Insulin stimulated Na/K ATPase so if there is a deficiency or insensitivity there is potential for hyperkalemia (But average diabetic not hyperkalemic because of beta-adrenergic and aldosterone effects)

Note: If patient has significant hyperglycemia, in addition to insulin deficiency the patient also has movement of water from inside to outside of cell. Glucose doesn't enter most cells easily, which increases EC osmolality and tonicity. K+ leaks out of the cell.

3. Beta adrenergic blockade
    a. Subjects treated with propanolol developed higher levels of K+ afterload
4. Increased tissue breakdown ex. Rhabdomyolysis
5. Exercise
    a. K+ channels in muscle cells closed because of ATP, but during exercise you use up ATP so channels open, resulting in K+ leakage
    b. Not a bad thing because K+ acts locally as a vasodilator which increases blood supply to working muscle (K+ can be increased to 0.5 to 1.0mEq/L with strenuous exercise)

C. Reduced K+ excretion in urine

1. Deals with how well nephron functions or presence of aldosterone

2. Can be due to decreased Na+ delivery (no electron sink for K+ or H+ formed) seen in advanced renal failure, circulatory shock or severe CHF, then glomerular filtrate will be absorbed proximally
3. Any problem with aldosterone will limit K+ handling ability due to hypereninemic hypoaldosteronism, use of ACE inhibitors (inhibit formation of Angio II), K+ sparing diuretics, and primary adrenal insufficiency

V. Causes of hypokalemia (Table 7.4 p 184)
   A. Markedly diminished intake—generally not a cause
   B. If K+ moves from EC to IC compartment there will be a change in serum K+ concentration, as seen in metabolic alkalosis or increased beta adrenergic activity
      1. Metabolic alkalosis—deficiency of H+ in EC compartment due to increase in bicarbonate. H+ leaves to EFC to normalize pH. Na/K pump keeps Na out therefore K+ enters cell

Note: If metabolic alkalosis and high bicarbonate present, this promotes more K+ wasting in distal tubule in at least the first week.

      2. Beta adrenergic activity—stimulation results in quicker K+ uptake which can lead to hypokalemia
   C. Lose K+ in GI tract via diarrhea, vomiting, or tube drainage
      1. With vomiting the loss is not directly form gastric secretions because K+ concentrations in upper GI juices is low, but by losing H+ via vomiting creates metabolic alkalosis
      2. With diarrhea, you can lose large amounts of GI fluids and thus large amounts of K+ (50-90mEq/L of K+ in lower GI)
      3. Depending on location of tube you can lose variable amounts of K+
   D. Increase urinary losses of K+
      1. Loop and thiazide diuretics act in area proximal to principal cells. They inhibit Na+ reabsorption in thick ascending limb of loop of Henle (loop diuretics), therefore more Na+ gets to distal areas and more K+ can be secreted
      2. Vomiting—there is a high bicarbonate level and until bicarbonate secreting cells are turned off, bicarbonate and K+ exit in urine
      3. Mineralocorticoid excess due to primary hyperaldosteronism or secondary hyperaldosteronism due to renal artery stenosis—leads to too much K+ secretion distally

Note: Licorice contains glyceratinic acid inhibits 11-beta-hydroxy steroid dehydrogenase which changes cortisol to cortisone in renal tubule. This results in large amounts of cortisol in tubular cells and this acts just like aldosterone giving rise to increased secretion of K+ in distal tubule.

      4. Renal tubular acidosis also leads to hypokalemia (Type I Distal and Type II Proximal, not Type IV)
         a. Type I is a problem with hydrogen ion secretion in distal tubule. Once can't maintain urine pH less than 6.5 (nl as low as 4.5). In type I, there are problems with Na+ reabsorption, back leak of H+ ions, or H+ ATPase is not active.

Normally H+ or K+ replaces Na+ as Na+ is reabsorbed. If H+ can't move, hypokalemia results.

b. In Type II proximal RTA, K+ is wasted from proximal tubule. The threshold is reduced from 26 to 14 or so. When bicarbonate stays low, the person is normal, but when given a bicarbonate load, most of it is lost in urine and results in increased delivery of bicarbonate to distal tubule (an impermeant ion) and this leads to increased K+ secretion.

VI. Why K+ is important

A. Best illustrated by looking at cardiac muscle cell

1. IC K+ concentration is 140mEq/L and EC K+ concentration is 4mEq/L therefore there is a large gradient for K+ movement
2. Resting ventricular muscle cell in diastolic phase, the cell is freely permeable to K+.
    a. Thus K+ moves from inside to outside cell. If this lasts long enough, IC negativity occurs.
    b. This creates resting membrane potential of –86mV.
3. Contraction of myocardial muscle requires a series of permeability changes in ventricular muscle
    a. If current comes down SA node → AV node → bundle of His → muscle, a small current is set up which causes a slight degree of depolarization.
    b. Resting membrane potential rises to –70mV and Na+ rushes into cell at threshold, which causes depolarization (less negative).
    c. K+ permeability decreases at this time. So cell is now positive with respect to EC compartment.
    d. Cell membrane then becomes permeable to calcium. Calcium moves into the cell, maintaining depolarization so muscle can contract for well over 100msec.
    e. Calcium permeability decreases. Cell membrane becomes permeable to K+ again and K+ exits cell and cell becomes negative—repolarization phase
    f. Need a period when sodium, calcium and K+ can normalize (pumps get rid of Na+, Ca2+ moves into mitochondria, and K+ moves back into cell)=repolarization phase
    g. The P wave of EKG=atrial contraction
    h. QRS wave=ventricular contraction
    i. T wave=repolarization
4. When action potential (AP) is generated, it causes activation/contraction coupling (contraction of myofibril) and stimulates AP in adjacent fibril.

5. The time it takes for QRS complex equals the time it takes for AP to propagate to entire cardiac muscle. So if conduction is slowed, the QRS complex is prolonged.
6. In hypokalemia—the EC concentration is low with normal IC K+ concentration, so concentration gradient is markedly increased. Depolarization occurs normally, but repolarization is different—cell permeability to K+ is decreased therefore repolarization is longer = flattened T wave and the production of a U wave
7. Effects of hypokalemia
   a. Lengthened P-R interval
   b. Flattened T wave
   c. Depressed S-T segment
   d. Presence of U waves
   e. Predisposition to ectopic atrial or ventricular beasts because repolarization takes longer and cell is not back to normal by the time a new impulse occurs.
8. In mild hyperkalemia, the resting membrane potential is not as negative because the gradient is not so great. Therefore cell is already partially depolarized before current arrives.
   a. It takes longer for AP to generate and it is not as high as it would be. Since gradient is less, cell increases permeability to K+ during repolarization. This gives rise to tall T waves and a QRS complex that is not as high.
9. In severe hyperkalemia, you see a marked decrease in AP height and a widening of the QRS complex because muscle doesn't contract as easily and AP doesn't spread from fibril to fibril as easily. Therefore it takes longer for excitation to go through cardiac muscle resulting in a prolonged QRS.
10. Fig 7.5 on p 182 shows normal serum K+ EKG and hyperkalemic EKG.
    a. With mild hyperkalemia, the peak T wave is the main change.
    b. At 8mEq/L, there is decreased height of QRS and the waves run together.
    c. At 12mEq/L, there is a sine wave. Treat this patient aggressively.
11. Cardiac effects of hyperkalemia
    a. Tall peak T waves
    b. Depressed S-T segment
    c. Decreased amplitude of R wave
    d. Prolonged P-R interval
    e. Decreased P wave
    f. Widening of QRS complex
    g. Prolongation of the Q-T interval

h. Other effects—bradycardia, hypertension, ventricular fibrillation, and cardiac arrest

Take home message: Keep serum K+ as normal as possible to keep cardiac muscle functioning optimally.

VII. Treatment of hyperkalemia

A. Acutely—treat with calcium so that cardiac action will be sustained. Calcium tends to counteract permeability changes in fibrils to keep reasonable cardiac contraction. Give 1 amp of calcium gluconate once and another amp 1 hr later.

B. Mobilize K+ into cell (effective in 15-30 minutes)

1. Glucose and insulin
2. Beta-adrenergic stimulation
3. Give sodium bicarbonate which gives rise to metabolic alkalosis

C. Increase loss of K+ from body (effective after several hours)

1. Give diuretics (PT MUST HAVE NORMAL KIDNEYS)
2. Use cation exchange resin
3. Dialysis