RENAL PHYSIOLOGY
SOLUTES, FLUID, AND BLOOD PRESSURE

Kenneth Alonso, MD, FACP

RENAL CIRCULATION

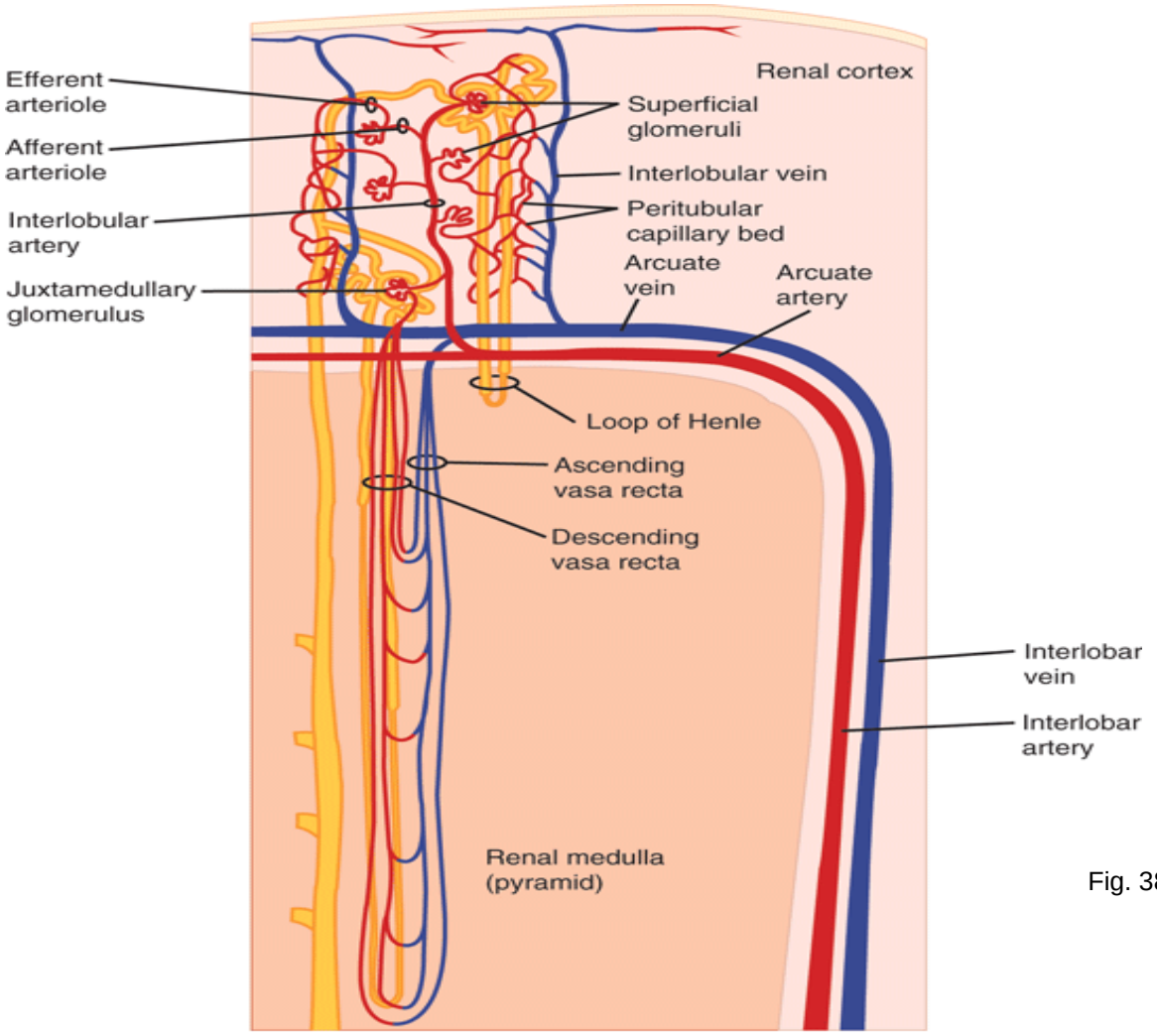


Fig. 38-3 Accessed 02/01/2010

Renal blood flow

- Sympathetic innervation to both efferent and afferent arterioles affects α-adrenergic receptors and leads to vasoconstriction.
- Both renal blood flow (RBF) and glomerular filtration rates (GFR) fall.
- Angiotensin II is a potent vasoconstrictor.
- As it effects efferent arterioles more than it does afferent arterioles, low levels produce an increase in GFR.
- High levels, decrease GFR.
- Arterial pressure is raised even at the expense of renal blood flow.

Angiotensin II

- Increases systemic vascular resistance:
- Stimulate vascular smooth muscle contraction
- Agument norepinephrine release.
- It causes the release of aldosterone from the adrenal cortex.
- Na^+ excretion is decreased by increasing Na^+ reabsorption by proximal tubules of the kidney.
- Opposed by atrial natriuretic peptide.
- It causes the release of vasopressin from the posterior pituitary gland, leading to water retention by the kidney.
- Opposed by atrial natriuretic peptide.

Angiotensin II

- Angiotensin II increases proximal tubular reabsorption
- Binds to receptors on the luminal and basolateral membranes
- Stimulate Na^+/H^+ antiporter
- Stimulate Na^+/HCO_3 cotransport
- Stimulate Na^+/K^+ ATPase activity.
- Increase interstitial fluid colloid osmotic pressure and decrease interstitial fluid hydrostatic pressure.

Angiotensin II

- Stimulate Na^+ reabsorption
- The loop of Henle
- The macula densa
- Distal nephron segments

Aldosterone

- Aldosterone stimulates Na^+ reabsorption and K^+ secretion.
- (1) Aldosterone binds to mineralocorticoid receptors
- Stimulate synthesis or activation of the Na^+-K^+-ATPase pump on the basolateral epithelial membrane
- These effects on the genome are mediated by activation of gene transcription and require 60 to 90 minutes to occur after administration of aldosterone.

Aldosterone

- (2) Aldosterone also exerts rapid nongenomic effects on the cardiovascular and renal systems.
- Aldosterone increases the Na^+ current in the cortical collecting tubule
- Activate the amiloride-sensitive Na^+ channel on the luminal side of the epithelial membrane.
- Stimulates the Na^+-H^+ exchanger in a <u>few minutes</u> after application.

Nitric oxide and renal function

- Reduced nitric oxide (NO) synthesis decreases pressure natriuresis and increases blood pressure.
- Decreased endothelial-derived nitric oxide synthesis impairs renal Na^+ excretory function
- Increase basal renal vascular resistance
- Enhance the renal vascular responsiveness to:
- Angiotensin II
- Norepinephrine
- Activate the renin–angiotensin system.

Nitric oxide and renal function

- Reductions in NO synthesis also impair sodium excretory function
- By directly increasing tubular reabsorption
- Or by altering intrarenal renal interstitial hydrostatic pressure or medullary blood flow.

Other controls of renal function

- TNF-α, IL-1, and endothelin-1 also function as vasoconstrictors.
- Activation of the endothelin-a receptor constricts, while the endothelin-b receptor dilates renal vessels.

Atrial natriuretic peptide

- Plasma levels of atrial natriuretic peptide are elevated in conditions associated with enhanced sodium excretion.
- Acute blood volume expansion consistently elevates circulating levels of atrial natriuretic peptide .
- Chronic increases in dietary sodium intake also raise circulating levels of atrial natriuretic peptide .

Renal blood flow

- Prostaglandins are produced locally in the kidney.
- Their production is stimulated by the same forces that stimulate sympathetic activity and angiotensin II production.
- They are vasodilatory and clearly protective of renal blood flow.
- Renal blood flow is unchanged between systemic blood pressures of 80-200 mmHg (Autoregulation).

Autoregulation of renal blood flow

- Arteriolar resistance is controlled at the level of the afferent arteriole.
- Reflex stretching of smooth muscle in blood vessel walls leads to intracellular Ca^{2+} release and increased tension.
- When RBF and GFR increase, increased solute and water delivery is sensed at the macula densa.
- Vasoactive substances (possibly adenosine) that constrict afferent arterioles is secreted, reducing RBF and GFR.

Autoregulation of renal blood flow

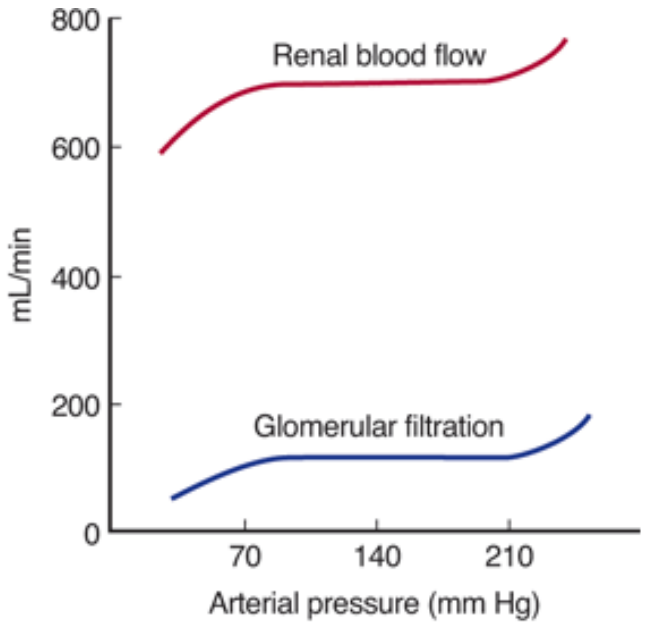
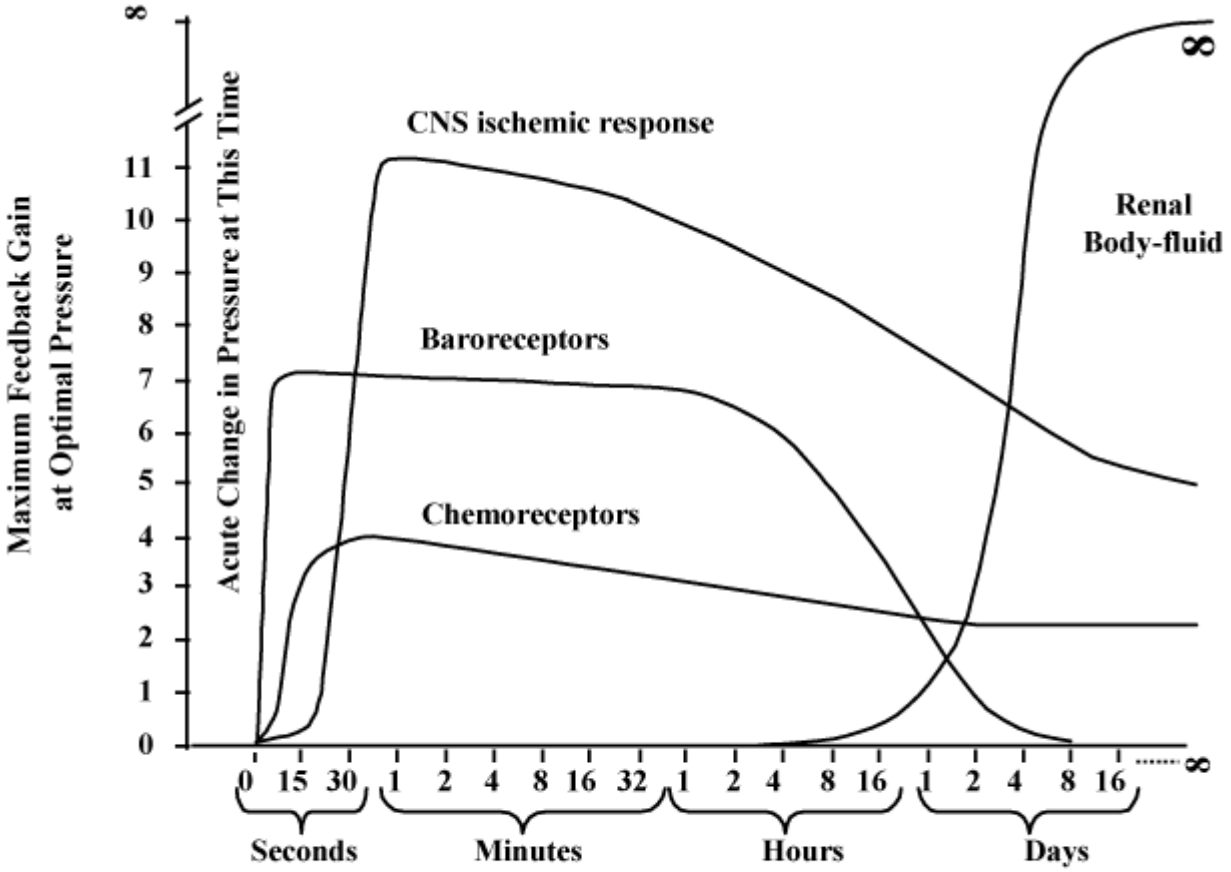


Fig. 38-4 Accessed 02/01/2010

Blood pressure control mechanisms



Source: Redrawn from Guyton AC, Hall JE. *Textbook of Medical Physiology,* 11th ed. Philadelphia: Elsevier, 2006, p. 230.

Fig. 69-3 Accessed 04/01/2010

GLOMERULUS

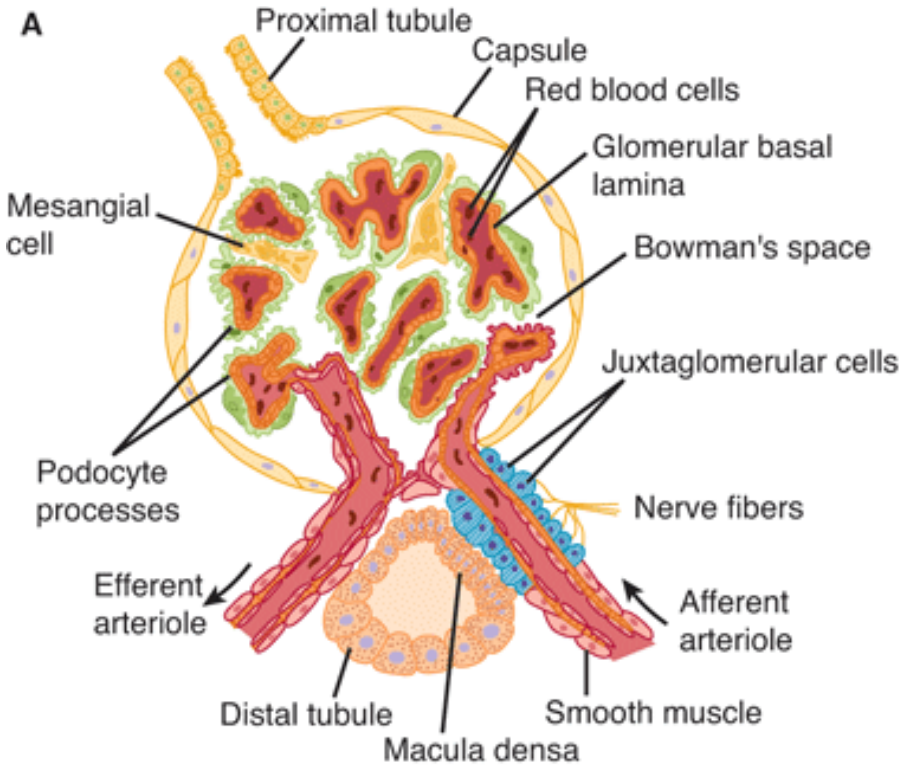


Fig. 38-2 Accessed 02/01/2010

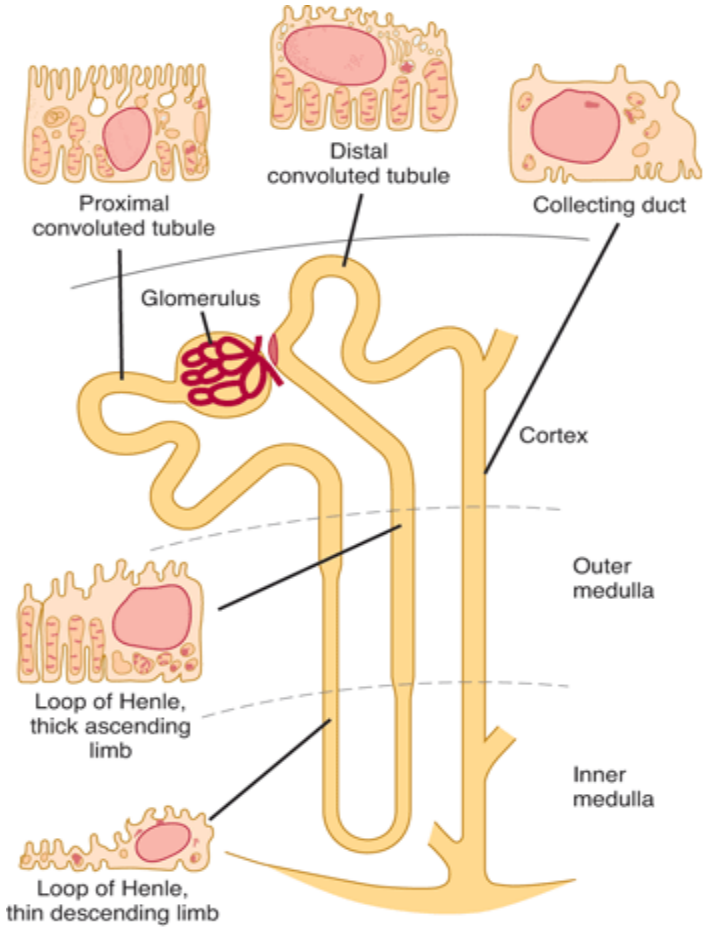
Glomerular filtration

- Filtration is dependent upon pore size and electric charge.
- The basement membrane, endothelium, podocytes, and foot processes are negatively charged.
- Fluid movement is directly related to:
- The water permeability or hydraulic conductance of the glomerular capillary wall
- The hydrostatic pressure in the capillaries
- Constant along its length in the glomerulus as opposed to the systemic circulation
- Is directly opposed by the hydrostatic pressure of fluid in Bowman's space as well as the oncotic pressure in glomerular capillaries.

Glomerular filtration

- Unfiltered plasma leaves the glomerular capillaries via efferent arterioles. and enters the peritubular space.
- As more fluid is filtered out of glomerular capillary blood, protein concentration and osmotic pressure increase in the peritubular space
- Favor the reabsorption of iso-osmotic fluid in the lateral intracellular space between the proximal tubules.
- Noted in extracellular fluid volume contraction

Juxtamedullary nephron



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 38-1 Accessed 02/01/2010

Major nephron segments

Segment	Function	Mechanism	Action of hormones
Early proximal tubule	**Iso-osmotic reabsorption** **1α hydroxylase converts vitamin D**	**Na+ cotransport with glucose, amino acids, phosphate** **Na+-H+ exchange**	**PTH inhibits Na+-phosphate cotransport** **Angiotensin II stimulates**
Late proximal tubule **(no glucose, amino acid, little bicarbonate ion; high Cl- concentration)**	**Iso-osmotic reabsorption**	**NaCl reabsorption driven by Cl- gradient**	

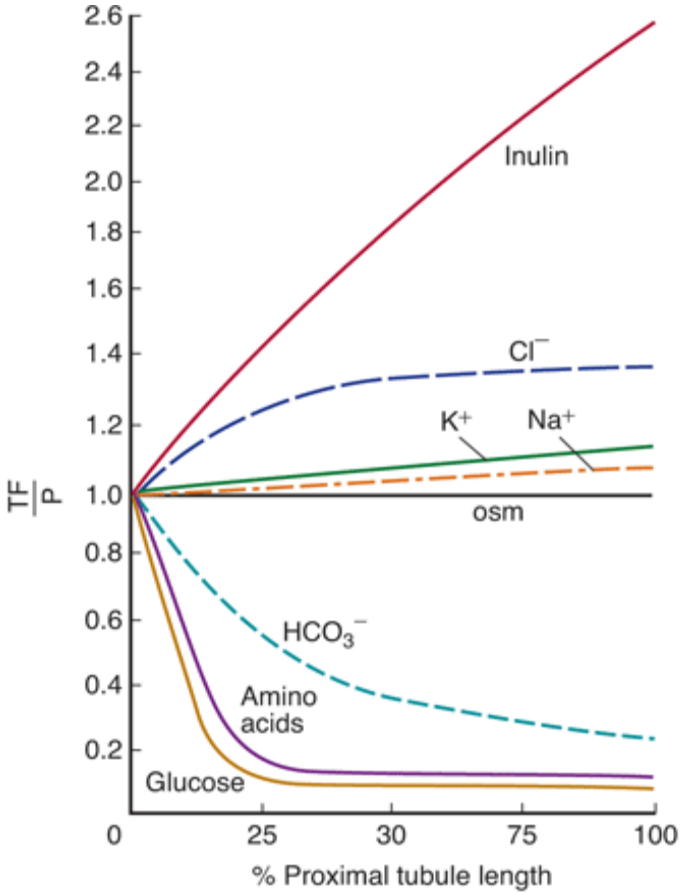
MAJOR NEPHRON SEGMENTS

Segment	Function	Mechanism	Action of hormones
Thick Ascending Limb of the Loop of Henle **(load dependent)** **(impermeable to water)**	**Reabsorption of NaCl without water dilution of tubular fluid** **Single effect of countercurrent multiplication** **Reabsorption of Ca^{2+} and Mg^{2+} driven by lumen-positive potential**	**Na+-K+-2Cl- cotransport**	**ADH stimulates**
Early distal tubule **(load dependent)** **(impermeable to water)**	**Reabsorption of NaCl without water** **Dilution of tubular fluid**	**Na+-Cl- cotransport**	**PTH stimulate Ca^{2+} reabsorption**

Major nephron segments

Segment	Function	Mechanism	Action of hormones
Late distal tubule and collecting ducts (principal cells)	Reabsorption of NaCl K+secretion Variable water reabsorption	Na+ channels K+ channels Water channels	Aldosterone stimulates Aldosterone stimulates Aldosterone and ADH stimulate
Late distal tubule and collecting cells (α-intercalated cells)	Reabsorption of K+ Secretion of H+	H+-K+ ATPase H+ ATPase	 Aldosterone stimulates

Reabsorption of solutes in the proximal tubule.



TF/P, tubular fluid:plasma concentration ratio.

(Courtesy of FC Rector Jr.)

Fig. 38-9 Accessed 02/01/2010

Extracellular fluid

- In the steady state, intracellular osmolality is the same as extracellular osmolality.
- To maintain this equality, water shifts freely across cell membranes.
- Large solutes such as NaCl, $NaHCO_3$, and large sugars are confined to the extracellular fluid.
- Adjustment of osmolality of excreted urine occurs in the vasa recta of the kidney.

Iso-osmotic gains and losses

- If 0.9% saline is infused, the fluid gained is iso-osmotic.
- Extracellular fluid volume increases
- Decreased hematocrit, total protein because of dilution
- Intracellular fluid volume as well as osmolality does not change.

Iso-osmotic gains and losses

- In diarrhea or with burns,
- The fluid lost is iso-osmotic.
- Extracellular fluid volume diminishes
- Increased hematocrit, total protein because of volume contraction
- Intracellular fluid volume as well as osmolality does not change.

Hyper-osmotic gains and losses

- With high salt intake,
- The extracellular fluid volume expands as the fluid gained is hyperosmotic
- Decreased total protein as volume contracts
- Hematocrit also decreases as water shifts from cell, MCV falls
- Intracellular fluid volume decreases. Osmolality is increased.

Hyper-osmotic gains and losses

- With sweating, fever, or in diabetes insipidus
- Salt is lost
- Hyperosmotic fluid loss
- Extracellular and intracellular fluid volumes fall.
- Osmolality increases.
- Total protein increases because of volume contraction;
- however, hematocrit does not change as water shift from cell reduces rbc size (MCV falls).

Hypo-osmotic gains and losses

- With SIADH,
- Water is retained (hypo-osmotic fluid).
- Extracellular fluid volume expands
- Total protein decreases by dilution
- Hematocrit remains unchanged as dilution offset by water shift into cell, increasing rbc size (with rise in MCV).
- Intracellular fluid volume increases.
- Osmolality decreases.

Hypo-osmotic gains and losses

- With adrenal insufficiency,
- Na^+ is lost (hypo-osmotic fluid)
- Extracellular fluid volume decreases
- Increased total protein as volume contracts
- Hematocrit also increases by water shift into cell, increasing rbc size (with rise in MCV).
- Intracellular fluid volume increases.
- Osmolality is elevated.

Hypovolemia

- Orthostatic hypotension or orthostatic tachycardia point to hypovolemia.
- Fractional excretion of urea (FE_{urea}) is <55% or FE_{Na+} <0.5%.
- The usual causes are:
- Salt loss with free-water intake (vomiting, diarrhea, burns)
- Diuretics
- Renal disease
- Adrenal insufficiency.

Hypervolemia

- Edema, ascites, jugular venous distention, or an S_3 gallop point to hypervolemia.
- The usual causes are:
- Heart failure
- Cirrhosis
- Nephrotic syndrome.

Evaluation of fluid loss

- Auscultatory blood pressures 4-15 mmHg below direct systolic blood pressure measurement, and 3-6 mmHg above direct diastolic blood pressure measurement suggest hypovolemia.
- 2-4% normovolemic individuals increase pulse >30 beats per minute when moving from supine to standing. (>20 bpm if sitting to standing).
- Useful screen in blood loss.
- In patients thought to be dehydrated, a urine specific gravity >1.020 is associated with a positive likelihood ratio, LR+, of 11, while the LR- is 0.1 for hypovolemia.

Evaluation of fluid loss

- Dry axilla in elderly (LR+ 2.8, LR- 0.06)
- Pulse increment even though the BUN/creatinine ratio is <25 and serum osm is >295 mosm (LR+ 1.7 LR- 0.8) are suggestive for hypovolemia unrelated to blood loss.
- In children, capillary refill time >2s, and the presence of dry mucous membranes or absent tears is strongly associated with dehydration (LR+ 6.1, LR- 0.24).

Evaluation of fluid loss

- Loss of up to 15% of circulating volume (750 ml in an 70 kg adult) may not be associated with alteration in heart rate, blood pressure, respiratory rate, or urine output.
- Pulse pressure may be increased.
- Loss of 15-30% of circulating volume (750–1500 ml) is usually associated with elevated heart rate (>100) and respiratory rate.
- Blood pressure may still be normal though the pulse pressure is decreased.
- Urine output begins to fall (<30 ml/min).
- The patient may be mildly anxious.

Evaluation of fluid loss

- Loss of 30-40% of circulating volume (1500-2000 ml) is usually associated with significantly elevated heart rate (>120) and respiratory rate (>30).
- Blood pressure and pulse pressure are decreased.
- Urine output falls (<15 ml/hr).
- The patient may be anxious, confused.

Evaluation of fluid loss

- Loss of >40% of circulating volume (>2000 ml) is usually associated with a very elevated heart rate (>140) and respiratory rate (>30).
- Blood pressure and pulse pressure are decreased.
- Urine output is negligible.
- The patient may be confused and lethargic.

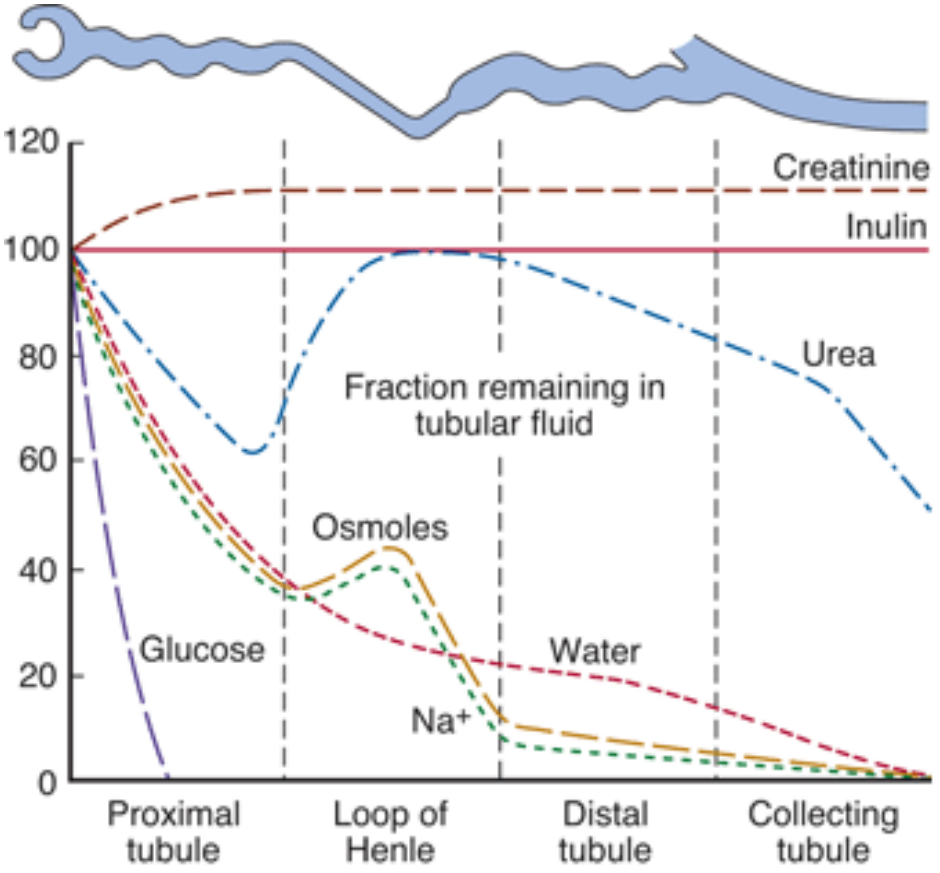
Volume status

- The usual causes of a low Na^+ with normal circulating volume:
- Carbamazepine (20-30% of patients
- SIADH (cancer, 15% of patients)
- Chlorpropamide (7-8% of patients)
- Hypothyroidism
- Inadequate ACTH production
- Ecstasy
- Strenuous exercise
- Psychogenic polydipsia
- Cortisol and hyponatremia both suppress ADH.

Volume status

- Total body water (TBW) = 0.6 (men, but 0.5, women) x weight in kg (men)
- Change in Na+ per liter of solution infused: (Infusate $_{Na+}$ - Plasma $_{Na+}$)/ (TBW + 1)
- Target change of 0.5 mEq/L/hr

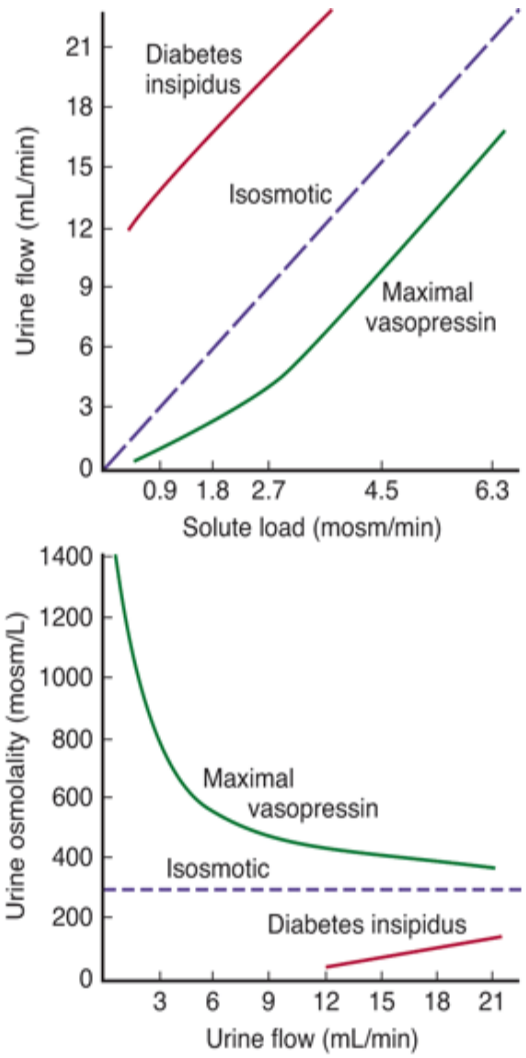
Vasopressin effect on filtration



(Modified from Sullivan LP, Grantham JJ: *Physiology of the Kidney,* 2nd ed. Lea & Febiger, 1982.)

Fig. 38-14 Accessed 02/01/2010

Osmotic pressure and urine flow



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Berliner RW, Giebisch G in: *Best and Taylor's Physiological Basis of Medical Practice,* 9th ed. Brobeck JR (editor). Williams & Wilkins, 1979.)

Fig. 38-18 Accessed 02/01/2010

Acid-base balance

- The cells of the proximal and distal tubules secrete hydrogen ions.
- Acidification also occurs in the collecting ducts.
- The reaction that is primarily responsible for H^+ secretion in the proximal tubules is Na^+–H^+ exchange.
- Na^+ is absorbed from the lumen of the tubule and H^+ is excreted.

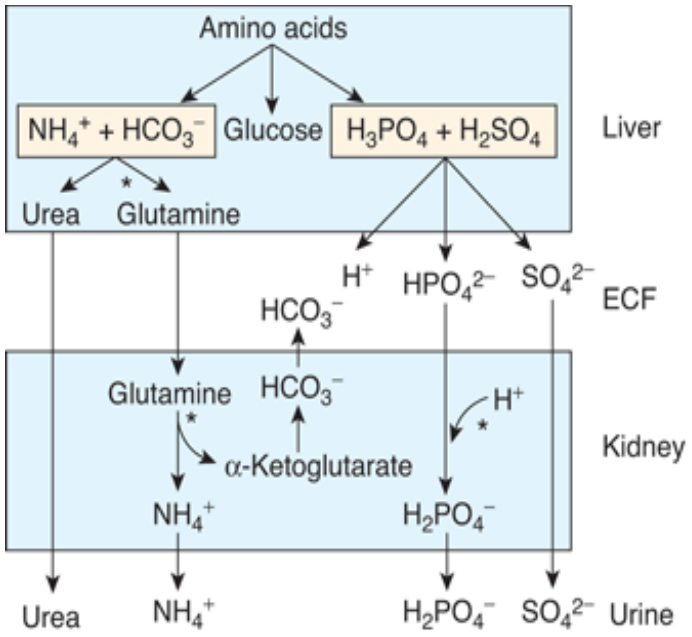
Acid-base balance

- The maximal H^+ gradient against which the transport mechanisms can secrete in humans corresponds to a urine pH of about 4.5.
- Three important reactions in the tubular fluid remove free H^+ permitting more acid to be secreted:
- HCO_3^- to form CO_2 and H_2O
- HPO_4^{2-} to form $H_2PO_4^-$
- with NH_3 to form NH_4^+.

Acid-base balance

- Carbonic anhydrase catalyzes the formation of H_2CO_3, and drugs that inhibit carbonic anhydrase depress secretion of acid by the proximal tubules.
- Renal acid secretion is altered by changes:
- In the intracellular pCO_2
- K^+ concentration
- Carbonic anhydrase level
- Adrenocortical hormone concentration.

Disposition of metabolically produced acid loads.



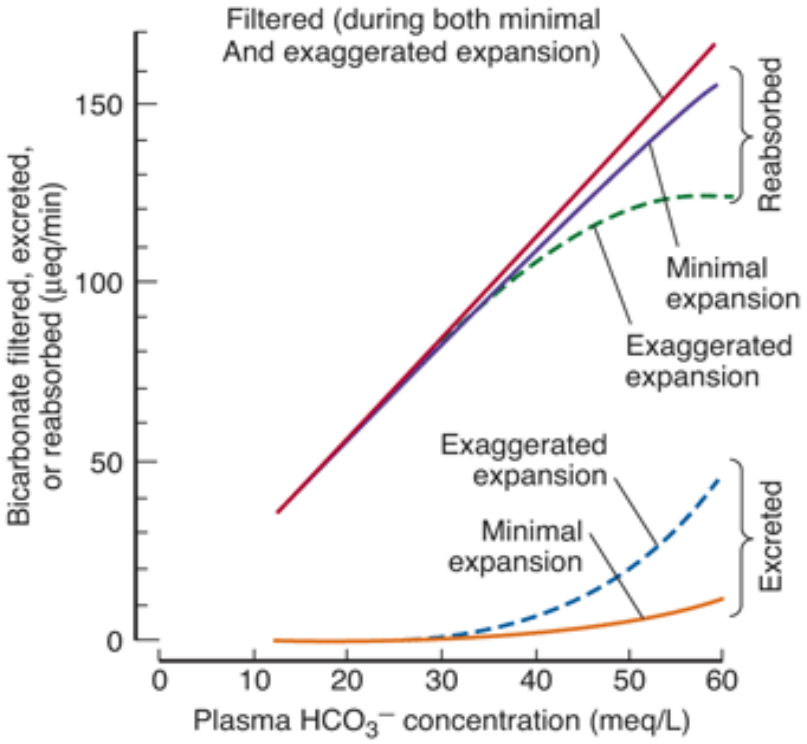
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Sites where regulation occurs are indicated by asterisks.

(Modified and reproduced with permission from Knepper MA, et al: Ammonium, urea, and systemic pH regulation. Am J Physiol 1987;235:F199.)

Fig. 40-5 Accessed 02/01/2010

Extracellular fluid volume and its effects on bicarbonate



(Reproduced with permission from Valtin H: *Renal Function,* 2nd ed. Little, Brown, 1983.)

Fig. 40-4 Accessed 02/01/2010

Regulation of elevated Na^+

- Extracellular fluid volume expands as the fluid gained is hyperosmotic.
- Intracellular fluid volume decreases.
- Osmolality is increased.
- In response, sympathetic activity decreases
- Dilate afferent arterioles
- GFR increases
- Decrease in protein concentration in peritubular tissues.
- Na^+ reabsorption falls in proximal tubules.

Regulation of elevated Na^+

- Atrial natriuertic peptide (ANP) and angiotensin II constrict efferent arterioles
- GFR increases
- Na^+ reabsorption falls in collecting ducts (ANP)
- Na^+ reabsorption falls in proximal tubule
- Angiotensin II stimulates aldosterone, production

Regulation of elevated Na^+

- Dopamine is a natriuretic hormone.
- It increases Na^+ excretion through signal transduction by mediating the synchronized downregulation of basolateral Na^+/K^+-ATPase and apical Na^+/H^+ antiporter isoform-3 (NHE3) after binding to D_1 and D_2 receptors in the nephron.

Regulation of low Na^+

- With sweating, fever, or in diabetes insipidus, salt is lost
- Hyperosmotic fluid loss
- Extracellular and intracellular fluid volumes fall.
- Osmolality increases.
- Sympathetic activity increases
- Constrict afferent glomerular arteries
- Increases GFR
- Increases protein concentration in peritubular fluid
- Na^+ reabsorption increases in proximal tubules.

Regulation of low Na^+

- Atrial natriuretic peptide and angiotensin II levels fall
- Leads to relative dilatation of efferent arterioles
- GFR falls
- Na^+ reabsorption decreases in collecting ducts (ANP effect)
- Na^+ reabsorption decreases in proximal tubules
- Angiotensin II stimulates production of aldosterone.

Renin-angiotensin response

- Increased extracellular fluid volume leads to increased stroke volume.
- To maintain homeostasis (and a stable cardiac output) peripheral resistance falls through expansion of venous capacitance vessels (the micro-circulation).
- Renal blood flow decreases and delivery of Na^+ and K^+ to renal tubules increases.
- Salt and water are lost.
- Renin secretion is impaired; angiotensin production falls.
- Aldosterone secretion is not augmented.

Renin-angiotensin response

- Decreased extracellular fluid volume leads to a decrease in systemic arterial pressure.
- To maintain homeostasis, renal sympathetic nerve activity increases, resulting in renal arteriolar vasoconstriction, further diminishing glomerular capillary blood flow and delivery of Na^+ and K^+ to renal tubules.
- Renin release increases; angiotensin production is stimulated.
- This leads to systemic vasoconstriction and a rise in arterial pressure.
- The production of aldosterone increases, enhancing renal tubular absorption of Na^+, water retention, and restoration of extracellular fluid volume.

Hyponatremia

- If dilutional
- Restrict salt and water intake
- Diurese.
- Hypovolemic hyponatremia.
- Hyperglycemia as cause
- Elevated serum osmolality
- Correct blood sugar.

Hypovolemic hyponatremia

- <u>If secondary to increased ADH</u>
- Serum osmolality low (normally, 275-295mOsm/kg)
- Restrict water intake
- Treat underlying cause
- In chronic cases, demeclocyline may be administered.
- Na^+ replacement of should not be >0.5mEq/L/hr.
- Central pontine myelonlysis may cause a “locked-in” syndrome.

Hypervolemic hypernatremia

- Excessive Na^+ administration
- Mineralicorticoid excess.

Hypervolemic hypernatremia

- Urine osmolality <300mOsm/kg
- Compatible with diabetes insipidus
- Vasopressin administration will correct central diabetes inspidus, not nephrogenic diabetes insipidus.
- Nephrogenic diabetes insipidus is treated with Sodium restriction and thiazide diuresis.
- Urine osmolality >600mOsm/kg indicates extrarenal water loss.

Hypokalemia

- Presents with weakness, muscle cramps.
- May see U waves on EKG.
- AV block and ventricular ectopy may also be noted.
- Urinary Potassium >30mEq/L indicates renal losses.
- <u>May also be Magnesium deficient.</u>

Hypokalemia

- If hypertensive, examine for:
- Hyperaldosteronism
- Cushing’s syndrome
- Licorice ingestion
- If normotensive, blood pH<7.4
- Suggests renal tubular acidosis.
- If hyperglycemic, diabetic ketoacidosis
- If normotensive, blood pH>7.4
- Suggests diuretics or vomiting as cause.
- Monitor with lead II if replacement >20mEq/L/hr.

Hyperkalemia

- May see small bowel ulcers.
- EKG shows peaked T waves
- Increased PR interval
- Widened QRS complex
- Progresses to sine wave pattern and cardiac arrest.
- Magnesium levels may also be low.

Hyperkalemia

- If GFR low, suggests renal failure as major contributory cause.
- If GFR normal, hypoaldosteronism.
- Associated with use of β-blockers, digoxin.
- May see with low insulin levels as well as in acidosis.
- If hypomagnesemia, correct.
- Hyperkalemia may spontaneously correct.

Hyperkalemia

- Calcium gluconate is administered as acute treatment.
- Acidosis is corrected with bicarbonate.
- The use of insulin is controversial.
- Treat with Kayexelate enema (Potassium binding resin)
- And diurese (or dialyze) as necessary.

ADH secretion

- Diabetes insipidus
- Presents with polyuria and polydypsia
- Serum Na^+ and osmolality increased
- Dilute urine
- ADH deficiency (central).
- Kidney unable to properly absorb water.
- Causes:
- Head trauma
- Tumors (principally craniopharyngioma)
- Meningitis

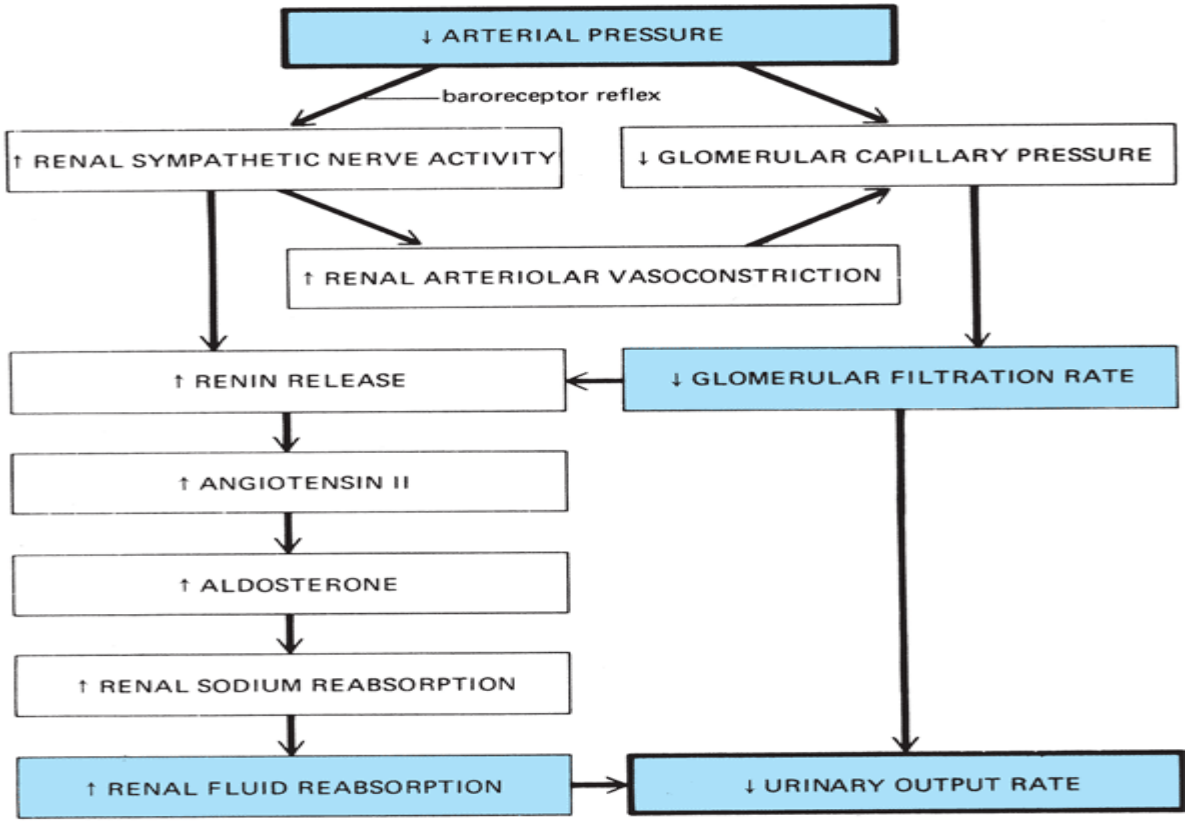
ADH secretion

- Syndrome of inappropriate ADH secretion.
- Excessive resorption of free water.
- Small cell carcinoma of the lung a common ectopic source of ADH production.
- Decreased Na^+
- Symptomatic when Na^+ approaches 130
- Cerebral edema.

Total body water

- Total body water is 60% of body weight in men, 50% in women.
- Intracellular fluid is 2/3 of total body water
- Interstitial fluid is ¼ of total body water
- Plasma is 1/12 of total body water
- Normal saline to increase intravascular volume
- Half-normal saline leads to water transfer from the extracellular fluid to intracellular space to equalize osmotic pressures in both compartments

Homeostatic mechanism



Source: Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6th Edition: http://www.accessmedicine.com

Fig. 9-9 Accessed 02/01/2010

Marked changes in fluid intake rate have rather minor influences on the arterial pressure of a normal individual.

Cardiovascular changes involved in postural change

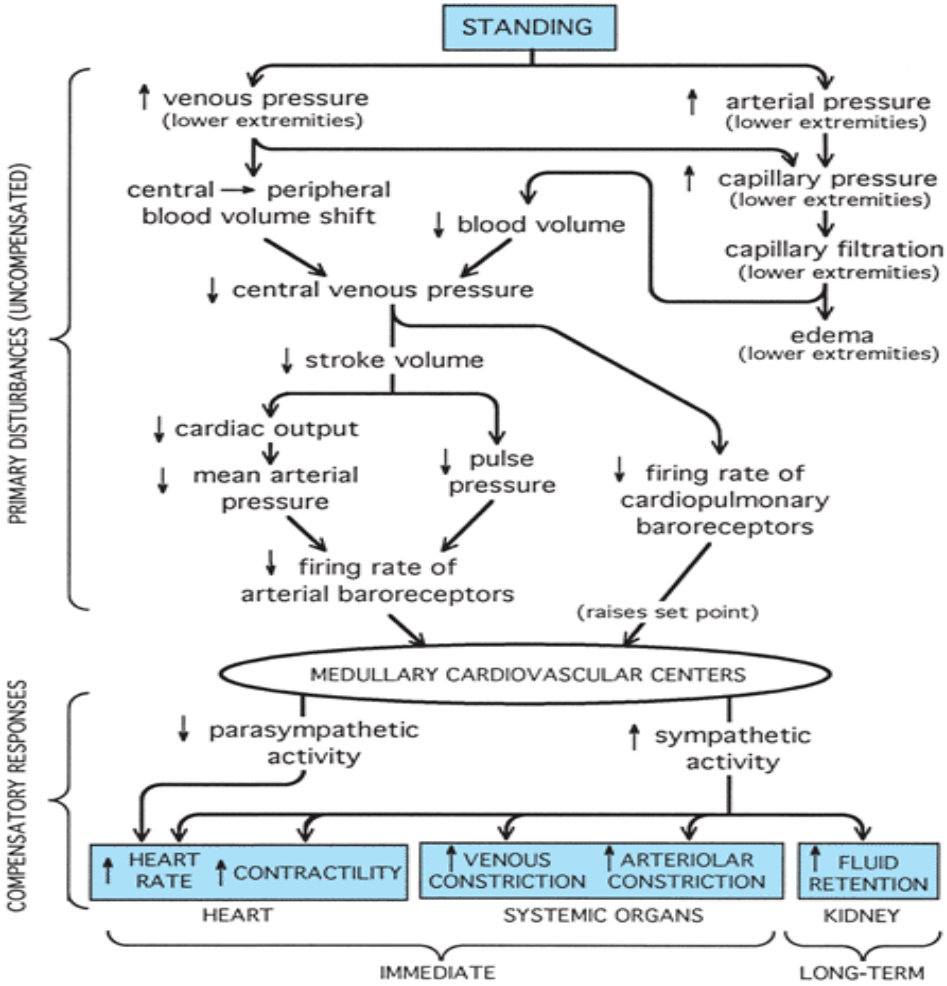


Fig. 10-3 Accessed 02/01/2010

Cardiovascular changes during exercise

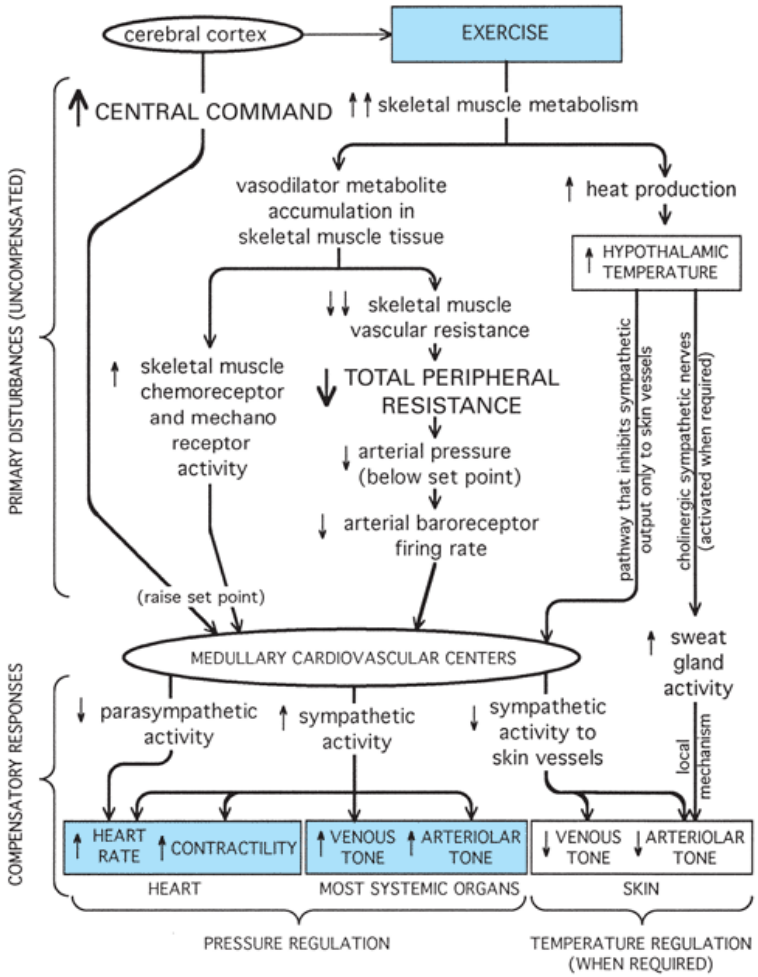


Fig. 10-5 Accessed 02/01/2010

Cardiovascular alterations in shock

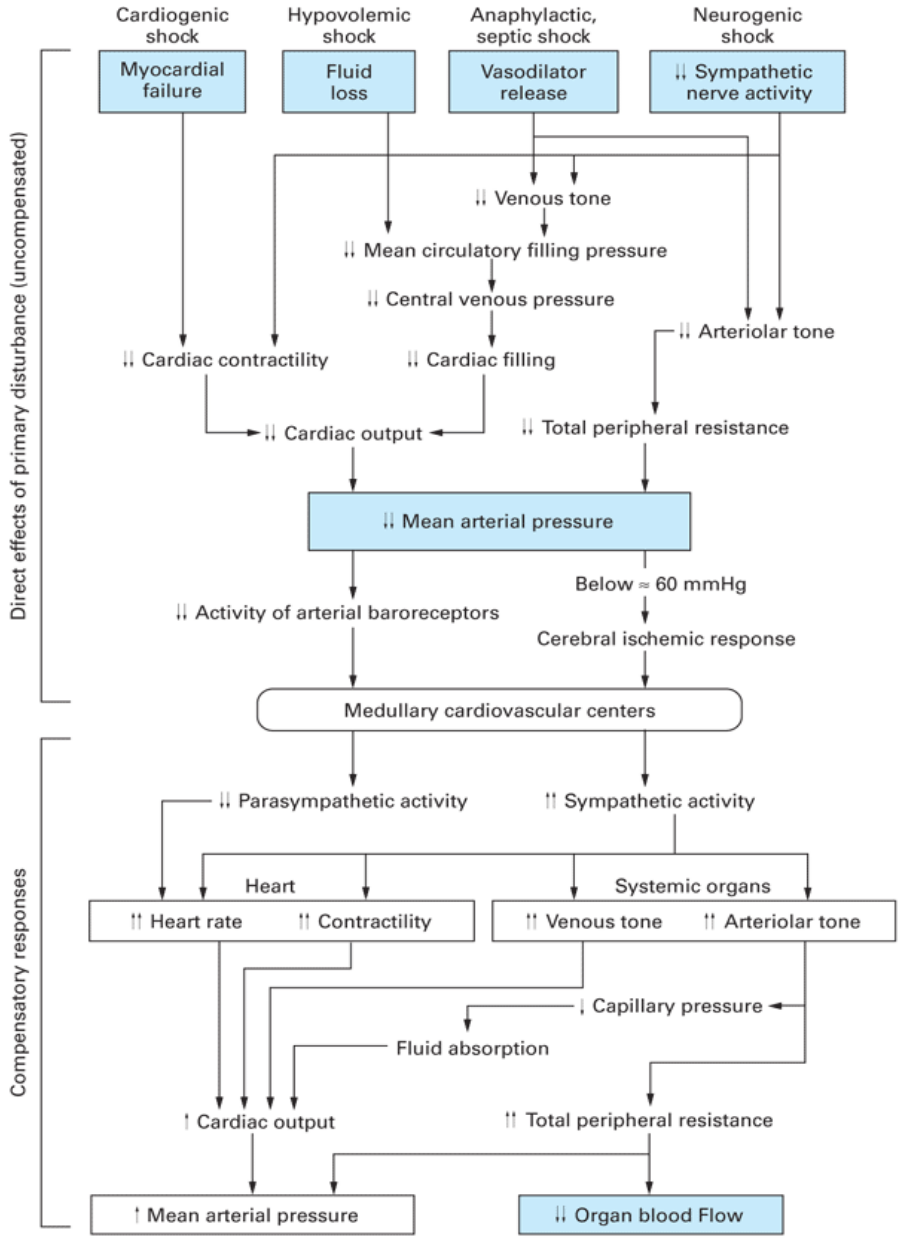


Fig. 11-1 Accessed 02/01/2010

Decompensated shock

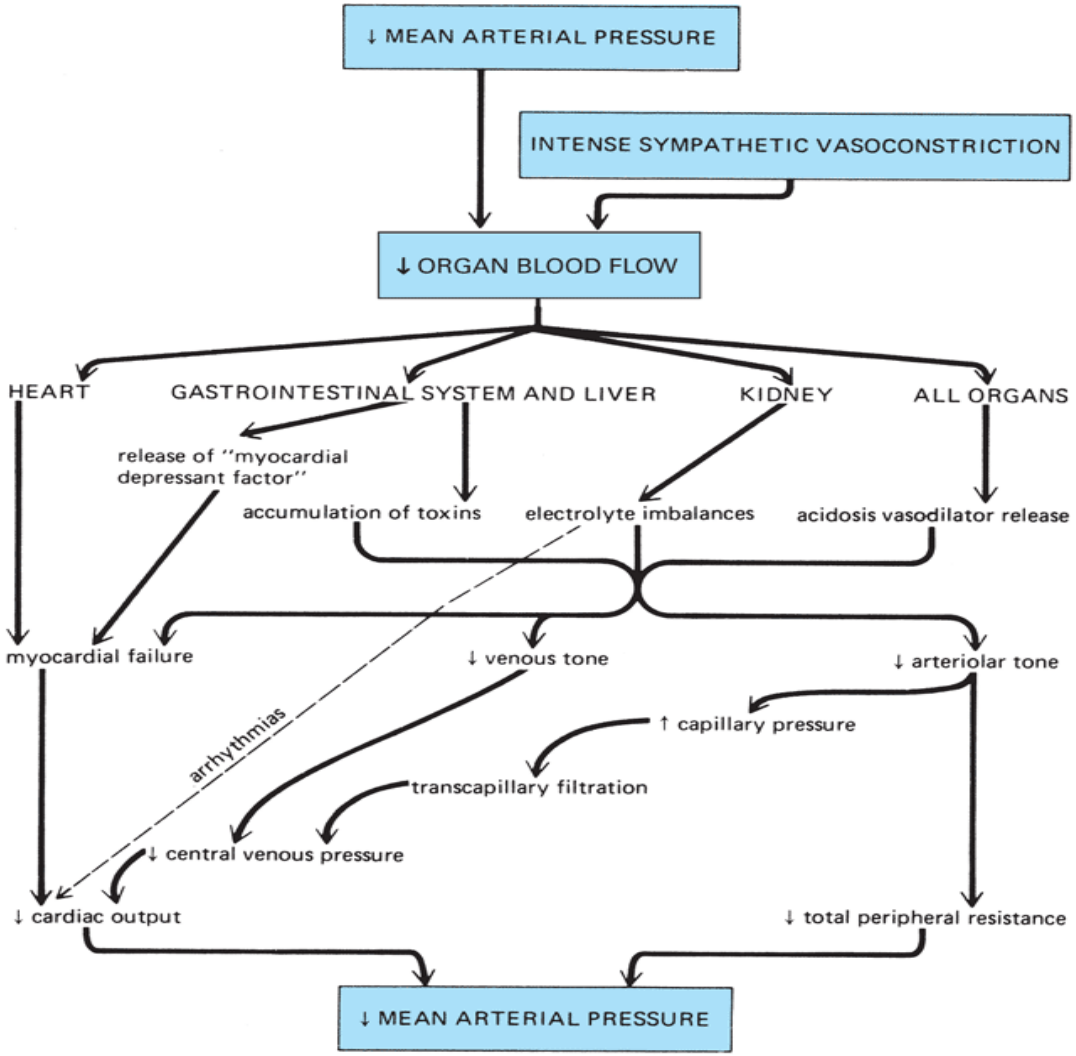


Fig. 11-2 Accessed 02/01/2010

Renal tubular acidosis

- Renal tubular acidosis 1 (distal)
- Inability to secrete H^+ at the distal tubule
- No new HCO_3^- can be generated.
- Unable to lower urine pH below 6.0
- Na^+, K^+, Ca^{2+}, PO_4^{3-}, SO_4^{2-} loss
- Stones comon
- Osteomalacia common

Renal tubular acidosis

- Renal tubular acidosis 2 (proximal)
- Impaired resorption of HCO_3^- in the proximal tubule.
- Na^+, K^+ lost
- No stones
- Renal tubular acidosis 3
- Combination of types 1 and 2

Renal tubular acidosis

- Renal tubular acidosis 4
- Decreased Na+ absorption as well as decreased H+ and K+ secretion in distal tubule
- Hypoaldosteronism

Renal function

- Specific gravity of first morning urine specimen best estimate of renal function.
- Concentrating ability is first function lost.
- Estimated GFR calculations are not accurate if GFR >60 ml/min or <25ml/min.
- Are useful to determine which patients require GFR determinations.
- Estimated GFR in a patient with stable creatinine: [(140 –age) x lean body weight in kg] / (Serum creatinine x 72).

Renal function

- Elevated Cystatin C identifies a preclinical state of kidney dysfunction that is not detected with serum creatinine or estimated glomerular filtration rate.

Renal function

- Chronic kidney disease is progressive.
- Renal failure shortens life.
- Life expectancy on dialysis varies from 10 years for those <30 years old to 2 years for those >45 years old.
- ACE inhibitors slow progression of kidney disease in both diabetic and non-diabetic patients.
- ACE plus angiotensin receptor blocker (ARB) may be optimal regimen.
- If no control with ACE plus ARB plus thiazide, screen for primary hyperaldsteronism.
- Avoid Cox-2 inhibitors, dihydropyridones.

Sodium

- Dehydration is suggested by elevated Na^+, urea Nitrogen (BUN), and relatively normal creatinine.
- Na^+ >150 suggests hypothalamic abnormality.

- Na^+ levels of 135 suggest diuretic use
- Normovolemic
- If dilutional (hypervolemic), responds to water restriction.

- Hyperglycemia is often the cause of hypovolemic hyponatremia (elevated serum osmolality noted).

Low sodium

- Na^+ <120 suggests inappropriate ADH secretion.
- Serum osmolality will be low.
- Causes:
- Ectopic ADH production
- Alcohol abuse
- Carbamazepine
- Valproic acid
- Li^+
- Li^+ uncouples receptor for vasopressin from G-protein, producing a nephrogenic diabetes insipidus.

Low sodium

- Responds to sodium restriction and thiazide diuresis.
- Responds to water restriction.
- Central pontine myelinolysis is a complication of too rapid an administration of Na^+ (>0.5mEq/L/hr).

Osmolality

- Calculated plasma osmolality:

  $2xNa^{+}$ + Glucose/18 + BUN/2.8 + alcohol/4.6

  Erroneously low if mannitol, sorbitol, ethylene glycol, methyl alcohol, isopropyl alcohol, excess lactate or ketoacids present

Osmolality

- In the normal patient, urine specific gravity varies directly with osmolality.
- This correlation is lost in the presence of glycosuria.
- A specific gravity of 1.010 is compatible with a urine osmolality of at least 350 mOsm/kg.
- This is the specific gravity of a plasma filtrate.
- Urine osmolality >600mOsm/kg indicates extrarenal water loss.

Potassium

- K^+ <3.5 associated with cardiac arrhythmia.
- Usually reflects diuretic use.
- Monitor with lead II if replacement >20mEq/L/hr.
- Low K^+ in the absence of diuretic use and in the presence of normal glomerular filtration rate suggests hyperaldosteronism or Cushing's syndrome.
- May also be hypertensive.
- Urinary K^+ >30mEq/L indicates renal losses.
- May also be Magnesium deficient.

Potassium

- If K^+ is low and the patient is normotensive, a blood pH<7.4 suggests renal tubular acidosis.
- If hyperglycemic, diabetic ketoacidosis
- If K^+ is low and the patient is normotensive, a blood pH>7.4 suggests diuretics or vomiting as cause.
- Elevated K^+ is seen in renal failure or patients on ACE inhibitors and spironolactone.
- Elevated K^+, LDH, and PO_4^{2-} (reported as phosphorous) suggest hemolyzed specimen used for testing.
- A change of pH by 0.10 alters K^+ levels by 0.5meq/L.

Chloride, Bicarbonate, Phosphate

- Cl^- levels low in chronic vomiting.
- HCO_3^- levels low in metabolic acidosis.
- HCO_3^- levels high in respiratory acidosis associated with chronic lung disease
- OR in metabolic alkalosis secondary to diuretic use.
- PO_4^{2-} levels (reported as phosphorous) are elevated in renal disease, myeloma, sarcoid.

Chloride, Bicarbonate, Phosphate

- Chloride/phosphorous ratio >30 in the fasting patient suggests hyperparathyroid disease.
- PTH decreases renal resorption of bicarbonate, increasing renal resorption of chloride, and phosphorus.

Creatinine

- Elevated creatinine is an indicator of renal impairment in patients with normal muscle mass.
- Creatinine is the end product of creatine metabolism
- Trimethoprim and cimetidine interfere with secretion of creatinine.
- Creatinine supplements are also associated with elevated levels of serum creatinine in the absence of renal impairment.

Creatinine

- Creatinine is filtered by the glomerulus and is not absorbed in the tubules.
- Timed creatinine clearance is a good estimate of renal function though with somewhat lower accuracy in the elderly.

Urea Nitrogen

- Urea, measured as Nitrogen, may be elevated in renal failure, gastrointestinal hemorrhage, or dehydration.
- The test is performed on serum but is reported as blood urea Nitrogen (BUN)
- Urea production removes ammonia generated by amino acid, pyrimidine, and purine catabolism in liver.
- Filtered by glomerulus and reabsorbed in proximal tubules when water is resorbed

Urea Nitrogen

- In the absence of acute renal failure, a BUN/creatinine ratio >20:1 suggests pre-renal disease.
- Hypovolemia
- Cardiac or liver failure
- Hemolysis or hemorrhage
- A normal ratio does not exclude acute tubular necrosis.

Urea Nitrogen

- A ratio <5:1 suggests intra-renal disease.
- Ischemia
- Nephrotoxic agents such as aminoglycosides
- Radiocontrast materials
- Myoglobin deposition
- Oxalate deposition (ethylene glycol ingestion)
- Low BUN in patient with renal failure is harbinger of hepato-renal syndrome.

Uric acid

- Completely filtered at the glomerulus.
- Accumulates in renal interstitium
- From which it is excreted as water is lost.
- No tubular reabsorption of uric acid.
- Elevated in patients with
- Gout
- Renal impairment
- Reflecting impaired clearance
- Malignancy
- Reflecting both production and impaired clearance

Uric acid

- Uric acid precipitation in tissue reflects saturation and is pH and temperature dependent.
- Alkalinizing the urine may accelerate excretion.