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USMLE™* Step 1

Lecture Notes

Physiology

*USMLE™ is a joint program of the Federation of State Medical Boards of the United States, Inc. and the National Board of Medical Examiners.

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Preface

These seven volumes of Lecture Notes represent the most-likely-to-be-tested material on the current USMLE Step 1 exam. Please note that these are Lecture Notes, not review books. The Notes were designed to be accompanied by faculty lectures—live, on DVD, or on the web. Reading these Notes without accessing the accompanying lectures is not an effective way to review for the USMLE.

To maximize the effectiveness of these Notes, annotate them as you listen to lectures. To facilitate this process, we've created wide, blank margins. While these margins are occasionally punctuated by faculty high-yield "margin notes," they are, for the most part, left blank for your notations.

Many students find that previewing the Notes prior to the lecture is a very effective way to prepare for class. This allows you to anticipate the areas where you'll need to pay particular attention. It also affords you the opportunity to map out how the information is going to be presented and what sort of study aids (charts, diagrams, etc.) you might want to add. This strategy works regardless of whether you're attending a live lecture or watching one on video or the web.

Finally, we want to hear what you think. What do you like about the notes? What do you think could be improved? Please share your feedback by E-mailing us at **medfeedback@kaplan.com**.

Thank you for joining Kaplan Medical, and best of luck on your Step 1 exam!

Kaplan Medical

SECTION I

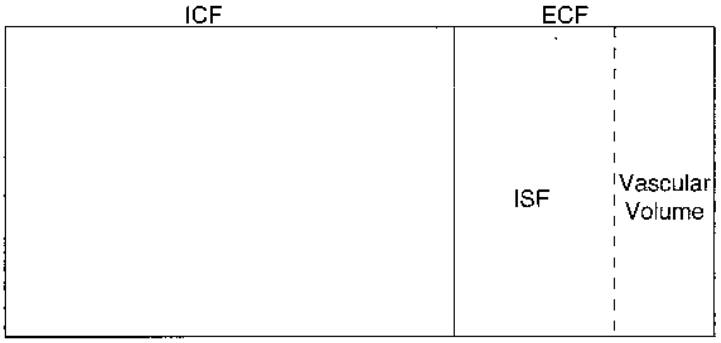
Fluid Distribution and Edema

Fluid Distribution and Edema

DISTRIBUTION OF FLUIDS WITHIN THE BODY

Total Body Water

- Intracellular fluid (ICF): Approximately 2/3 of total of body water
- Extracellular fluid (ECF): Approximately 1/3 of total body water
- Interstitial fluid (ISF): Approximately 2/3 of the extracellular fluid
- Total blood volume: Approximately 1/3 of the extracellular fluid is composed of plasma and the cellular elements of blood, primarily red blood cells



The solid-line division represents the cell membrane, and the dashed line capillary membranes.

Figure I-1-1

Intracellular Fluid (ICF) versus Extracellular Fluid (ECF)

Fluid distribution is determined by the osmotic movement of water. Osmosis is the diffusion of water across a semipermeable or selectively permeable membrane. Water will diffuse from a region of higher water concentration to a region of lower water concentration. The water concentration of a solution is determined by the concentration of solute. The greater the solute concentration is, the lower the water concentration will be.

The basic principles are demonstrated in Figure I-1-2.

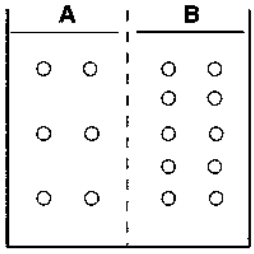


Figure I-1-2

This figure shows two compartments separated by a membrane that is permeable to water but not to solute. Side B has the greater concentration of solute (circles) and thus a lower water concentration than side A. As a result, water will diffuse from A to B, and the height of column B will rise, and that of A will fall.

It is the difference in the concentration of impermeable particles that determines the osmotic movement of water across the membrane. The concentration of these particles is often referred to as the effective osmolarity of a particular compartment. Because sodium chloride represents most of the nonpermanent particles of the extracellular fluid, the concentration of sodium chloride represents most of the effective osmolarity of this compartment. Other substances do contribute to the effective osmolarity, and the following formula is often used clinically to determine the overall effective osmolarity of the extracellular compartment:

$$\text{ECF Effective osmolarity} = 2(Na^+)\ \text{mEq/L} + \frac{\text{glucose mg \%}}{18} + \frac{\text{urea mg \%}}{2.8}$$

In most cases, two times the sodium concentration is a good index of extracellular osmolarity. However, this is not the case as in the hyperglycemia of an uncontrolled diabetic. Also, urea is freely permeable across most membranes and is usually not a consideration when estimating the ECF effective osmolarity.

- When the ECF effective osmolarity increases, cells always shrink.
- When the ECF effective osmolarity decreases, cells always swell.
- In a steady-state situation, the intracellular concentration of water equals the extracellular concentration of water. Thus, the intracellular and extracellular osmolarity are the same.

Units of concentration

mOsm (milliosmolar) or mOsm/L = an index of the concentration of particles per liter of solution

mM (millimolar) or mM/L = an index of the concentration of molecules dissolved per liter of solution

isotonic solutions = 300 mOsm = 150 mM NaCl (one NaCl molecule yields two particles in solution)

300 mOsm = 300 mM glucose

The 300 mOsm is rounded off from the true value of 285 to 290 mOsm.

Interstitial versus Plasma Fluid

Movement of fluid between these two compartments occurs across capillary membranes. Capillary membranes are freely permeable to all natural substances dissolved in the plasma, except proteins. Thus, it is the concentration of plasma proteins that determines the effective osmolarity between these two compartments. (Capillary exchange is discussed later in this section.)

Graphical Representation of Volume versus Solute Concentration in the ICF and ECF

It is important to understand how body osmolarity and the intracellular and extracellular volumes change in clinically relevant situations. Figure I-1-3 is one way of presenting this information. The *y* axis is solute concentration or osmolarity. The *x* axis is the volume of intracellular (2/3) and extracellular (1/3) fluid. If the solid line represents the control state, the dashed lines show a decrease in osmolarity and extracellular volume but an increase in intracellular volume.

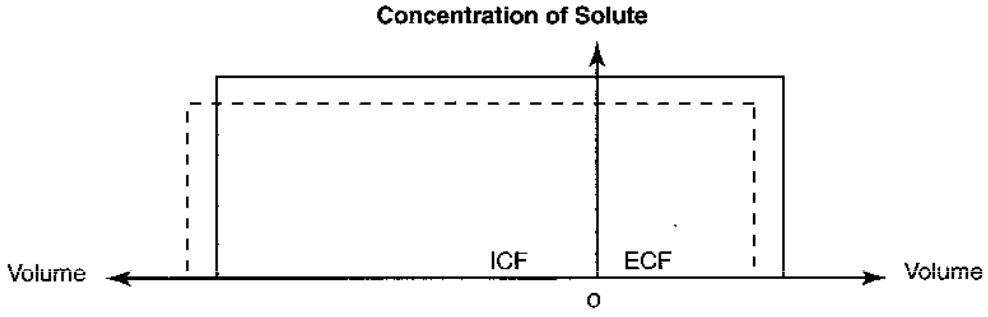


Figure I-1-3. Darrow-Yannet Diagram

Extracellular volume

When there is a net gain of fluid by the body, this compartment always enlarges. A net loss of body fluid decreases extracellular volume.

Concentration of solute particles

This is equivalent to body osmolarity and in most cases is approximated as twice the sodium concentration (mM) of the ECF. Remember, at equilibrium the intracellular and extracellular osmolarity will be the same.

Intracellular volume

This varies with the effective osmolarity of the extracellular compartment, that is, the concentration of particles that do not penetrate the cell membrane. An increase in osmolarity decreases intracellular volume, and the opposite occurs with a decrease in body osmolarity.

Review Questions

(Answers below)

Using the graph presented in Figure I-1-3, determine the volume and concentration changes associated with the following states of hydration.

1. Loss of isotonic fluid
   Examples: hemorrhage (neglect loss of ICF as red blood cell [RBC] volume), the formation of isotonic urine, and the immediate consequences of diarrhea or vomiting

2. Loss of hypotonic fluid
   Examples: sweating (dehydration), hypotonic urine formation such as occurs in diabetes insipidus and alcoholism

3. Ingestion of salt tablets

4. Person who drinks 1 liter of tap (or distilled) water (This is equivalent to water intoxication.)

5. Infusion of hypotonic saline (1/2 normal saline)

6. Infusion of isotonic saline

7. Infusion of hypertonic saline (or hypertonic mannitol)

8. Primary adrenal insufficiency (volume and salt depletion, volume replacement exceeds salt replacement)

Changes in volume and concentration (dashed lines)

1. Loss of isotonic fluid that might be due to hemorrhage (neglect loss of intracellular fluid as RBC volume), isotonic urine, or the immediate consequences of diarrhea or vomiting:

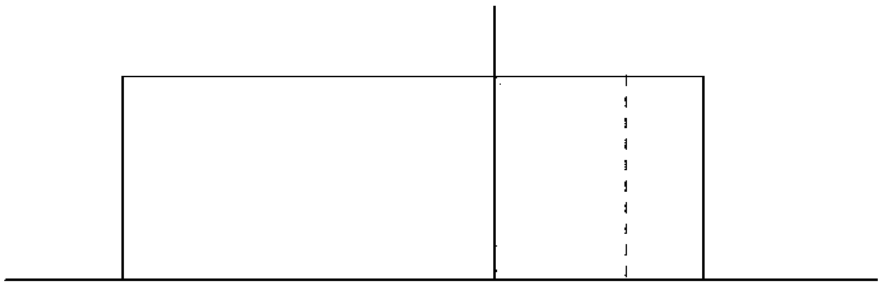


Figure I-1-4

There will be a loss of volume but no change in extracellular effective osmolarity. The fact that extracellular osmolarity is unchanged means no change in intracellular volume.

2. Loss of hypotonic fluid that might be due to sweating (dehydration), hypotonic urine, or diabetes insipidus:

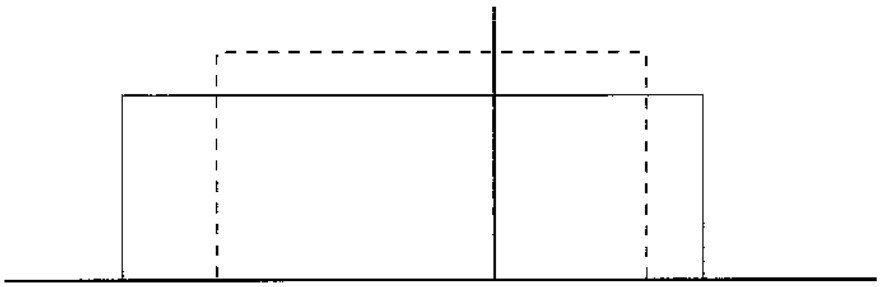


Figure I-1-5

Losing hypotonic fluid from the extracellular space would increase extracellular effective osmolarity (sodium concentration would increase). Fluid would move from the intracellular to the extracellular compartment until osmolarity was again equal in the two compartments. The fluid entering the extracellular space would partially but not completely compensate for the originate insult.

3. Ingestion of salt tablets:

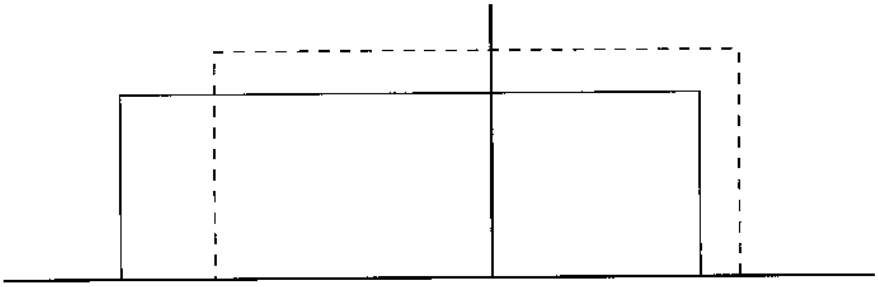


Figure I-1-6

The salt tablets would increase the effective osmolarity of the extracellular fluid. The result would be a fluid shift from the intracellular to the extracellular compartment.

4. Person who drinks 1 liter of tap (or distilled) water:

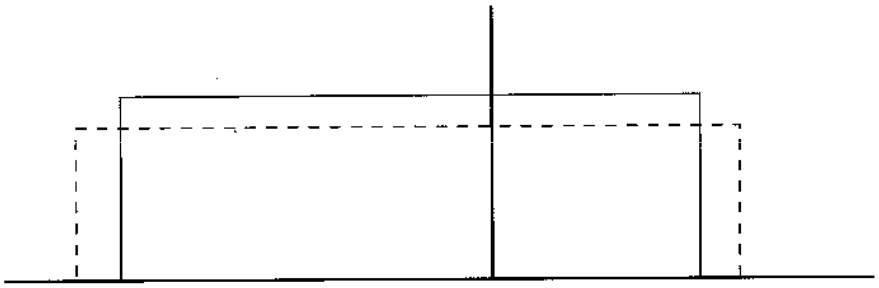


Figure I-1-7

The tap water entering the extracellular space would increase its volume and decrease its osmolarity. Because of the decrease in osmolarity, some of the ingested water would diffuse into the intracellular space.

5. Infusion of hypotonic saline (half-normal saline):

   The answer is the same as answer 4.

6. Infusion of isotonic saline:

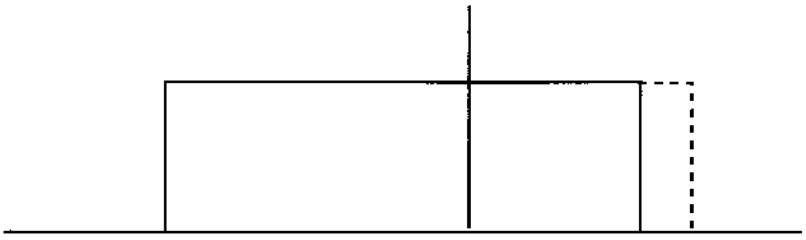


Figure I-1-8

The infusion of isotonic saline would increase the volume but not the effective osmolarity of the extracellular space. Because there was no change in osmolarity, the intracellular volume is unchanged. An additional point is that most of the saline would enter the interstitial space. A much smaller volume would remain in the intravascular compartment. If plasma, which does contain protein, was infused, however, almost all of the fluid would remain in the vascular space because the proteins do not easily cross capillary membranes.

7. Infusion of hypertonic saline (or hypertonic mannitol; mannitol does not cross cell membranes easily):

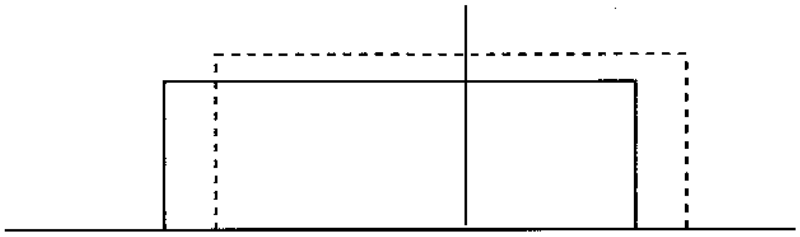


Figure I-1-9

The hypertonic saline would increase both the volume and effective osmolarity of the extracellular compartment. The increased osmolarity would cause a fluid shift from the intracellular to the extracellular space, reducing intracellular volume and further increasing extracellular volume.

8. Primary adrenal insufficiency:

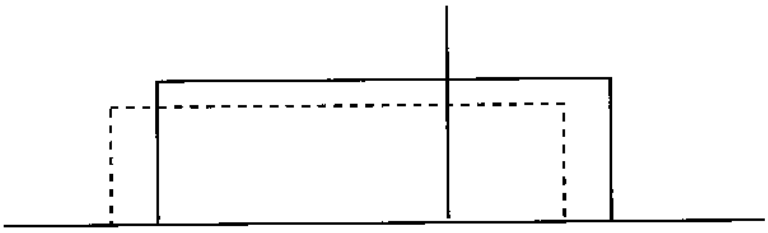
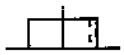
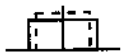
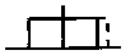
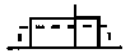
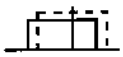


Figure I-1-10

This individual will lose both fluid and salt. There will be a partial dietary replacement of both fluid and salt but because fluid replacement exceeds salt replacement, body osmolarity remains below normal.

Table I-1-1. Summary of Volume Changes and Body Osmolarity Following Changes in Body Hydration

	ECF Volume	Body Osmolarity	ICF Volume	D-Y Diagram
Loss of isotonic fluid Hemorrhage Diarrhea Vomiting	↓	no change	no change	
Loss of hypotonic fluid Dehydration Diabetes insipidus Alcoholism	↓	↑	↓	
Gain of isotonic fluid Isotonic saline	↑	no change	no change	
Gain of hypotonic fluid Hypotonic saline Water intoxication	↑	↓	↑	
Gain of hypertonic fluid Hypertonic saline Hypertonic mannitol	↑	↑	↓	

ECF = extracellular fluid; ICF = intracellular fluid; D-Y = Darrow-Yannet

THE MICROCIRCULATION

General Characteristics

- Flow and pressure within the system are controlled by varying the radius (resistance) of the arterioles.
- Dilation of the arterioles causes an increase in flow and pressure in the capillaries, and constriction of the arterioles causes a decrease in pressure and flow in the capillaries.
- There are no major resistance vessels between the capillaries and veins; thus, an increase in venous pressure will be transmitted upstream to raise capillary pressure. For example, in left-sided heart failure the increase in left atrial pressure will cause a rise in pulmonary capillary pressure that promotes filtration and the development of pulmonary edema.
- Capillaries are generally permeable to all dissolved substances except plasma proteins. Even so, proteins slowly leak out into the interstitium.
- One function of the lymphatic system is the removal of interstitial proteins.

Filtration and Reabsorption

Filtration and reabsorption are the main processes by which fluid moves between plasma and interstitium. Filtration is defined as the movement of fluid from the plasma into the interstitium; reabsorption is movement of fluid from the interstitium into the plasma. These two processes are driven by osmotic and hydrostatic pressure differences and thus would be classified as bulk flow.

Figure I-1-11 illustrates the four factors that affect filtration and reabsorption.

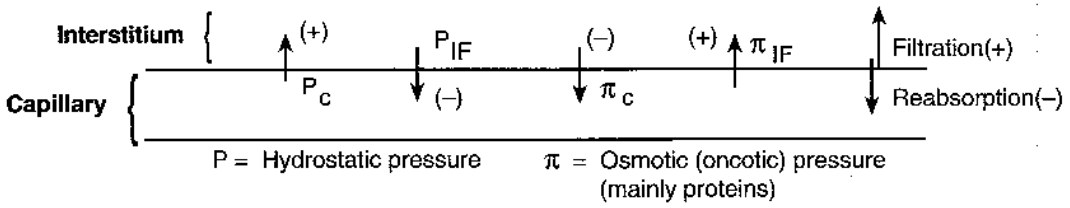


Figure I-1-11. Filtration Forces

P_C = hydrostatic pressure (blood pressure) in the capillary

Capillary hydrostatic pressure is increased by arteriolar dilation (upstream arterioles) and a rise in venous pressure. It is decreased by arteriolar constriction. Essential hypertension that is the result of an increase in TPR will raise blood pressure but lower the downstream capillary pressure. Hemorrhage will also lower capillary pressure and promote the reabsorption of interstitial fluid. Under most conditions, this is the main factor promoting filtration.

π_C = colloid osmotic pressure or oncotic pressure of plasma

This is the osmotic pressure of plasma solutes that cannot diffuse across the capillary membrane. The only natural substances are the plasma proteins, and the osmotic pressure is determined by the protein concentration in the plasma.

Capillary oncotic pressure is increased by dehydration, diarrhea, diuresis, or by the loss of any fluid that does not include the loss of protein. It is decreased by liver and renal disease (nephrotic syndrome) and by saline infusion (not plasma and whole blood, which contain protein). This is generally the main factor promoting reabsorption.

π_{IF} = determined by the concentration of protein in the interstitial fluid.

Normally the small amount of protein that leaks to the interstitium is removed by the lymphatics. Thus, under most conditions this is not an important factor influencing the exchange of fluid.

Interstitial oncotic pressure is increased by chronic lymphatic blockage and by greater capillary permeability to protein (e.g., burns).

P_{IF} = hydrostatic pressure in the interstitium

This pressure is difficult to determine. In most cases it is close to zero and is not a significant factor affecting filtration versus reabsorption. However, as we point out later, it can have a significant effect on filtration in the pulmonary circuit and in glomerular filtration in the kidney.

Clinically significant changes are mainly restricted to the pulmonary circuit. More negative thoracic pressures will increase filtration (e.g., respiratory distress syndrome).

These four forces are often referred to as Starling forces. Grouping the forces into those that favor filtration and those that oppose it, and taking into account the properties of the barrier to filtration, the formula for fluid exchange is the following:

$$Q_f = k\,[(P_c + \pi_{IF}) - (P_{IF} + \pi_C)]$$

Qf = fluid movement

k = filtration coefficient

This factor depends upon a number of factors but for our purposes the surface area for exchange is most important. For example, GFR in the kidney depends in part on the surface area of the glomerular capillaries. A loss of surface area can be compensated for only by an increase in capillary hydrostatic pressure; otherwise, GFR would decrease.

A positive value of Qf indicates net filtration; a negative value indicates net reabsorption. In some tissues (e.g., renal glomerulus), filtration occurs along the entire length of the capillary; in others (intestinal mucosa), reabsorption normally occurs along the whole length. In other tissues, filtration may occur at the proximal end and reabsorption at the distal end.

Questions

1. Given the following values, calculate a net pressure:

   P_C = 25 mm Hg
   P_{IF} = 2 mm Hg
   π_C = 20 mm Hg
   π_{IF} = 1 mm Hg

2. Calculate a net pressure if the interstitial hydrostatic pressure is –2 mm Hg.

Answers

1. +4 mm Hg
2. +8 mm Hg

VOLUME MEASUREMENT IN THE MAJOR FLUID COMPARTMENTS

Principle

To measure the volume of a body compartment, a tracer substance must be evenly distributed within that compartment. In this situation, the volume of the compartment can usually be calculated by using the following relationship:

$V \times C = A$, therefore $V = A/C$

V = Volume of the compartment to be measured

C = Concentration of the tracer in the compartment to be measured

A = Amount of the tracer

For example, if 300 mg of a dye was injected intravenously and at equilibrium, and the concentration in the blood was 0.05 mg/mL, the volume of the compartment that contained the dye would be:

Volume = 300 mg/ 0.05 mg/mL or 6000 mL.

This is called the volume of distribution (VOD), or the space of the test substance.

Required Properties of the Tracer

Tracers are generally introduced into the vascular compartment, and they will distribute through body water until they reach a barrier they cannot penetrate. The two major barriers encountered are capillary membranes and cell membranes.

Required criteria of tracers to measure the following compartments:

Plasma: not permeable to capillary membranes, e.g., albumin

ECF: permeable to capillary membranes but not cell membranes, e.g., inulin, mannitol, sodium, sucrose

Total body water: permeable to capillary and cell membranes, e.g., tritiated water, urea

Blood Volume versus Plasma Volume

Definition of blood volume

Blood volume represents the plasma volume plus the volume of RBCs, which is usually expressed as hematocrit (fractional concentration of RBCs).

Calculation of blood volume

The following formula can be utilized to convert plasma volume to blood volume:

$$\text{Blood volume} = \frac{\text{plasma volume}}{1 - \text{Hct}}$$

Hct = hematocrit

Example:

Hct = 50% (0.50)

Plasma volume = 3 L

$$\text{Blood volume} = \frac{3\text{L}}{1 - 0.5} = 6\text{ L}$$

Note that if the hematocrit is 0.5 (or 50%), the blood is half RBCs and half plasma. Therefore, blood volume will be double the plasma volume.

Distribution of intravenously administered fluids

- Vascular compartment: whole blood, plasma, dextran in saline
- ECF: saline, mannitol. At least 2/3 of the fluid would enter the ISF
- Total body water: D5W–5% dextrose in water. Once the glucose is metabolized, the water would distribute 2/3 ICF, 1/3 ECF.

Changes in Red Blood Cell Volume

Principle

Changes in red blood cell volume in an *in vitro* solution are due to the movement of water (osmosis) across the cell membrane. This is determined by the effective osmolarity (concentration of impermeable solutes) of the external fluid. Just remember, water will diffuse from a region of higher water concentration to a region of lower water concentration.

Effect of isotonic saline

If a normal RBC is placed in isotonic saline (300 mOsm NaCl), no change in red cell volume will occur. This is because the effective osmolarity of the solution equals the effective osmolarity inside the RBC. As long as the concentration of nonpenetrating particles of the external solution is 300 mOsm, there will be no significant change in the volume of the RBC.

Problems involving a nonpenetrating solute

Predict the changes in cell volume (increase, decrease, no change) when a normal RBC previously equilibrated in isotonic saline is placed in the following solutions. Assume the fluid volume of the external solution is large, and thus, as water moves in or out of the cell, there is no significant change in the concentration of beaker solutes (answers below).

1. 200 mOsm NaCl
2. 400 mOsm NaCl
3. 150 mM NaCl
4. 300 mM NaCl

Effect of substances that rapidly penetrate cell membranes

The presence of a substance, such as urea, that penetrates the cell membrane quickly does not affect the osmotic movement of water. If the total concentration of nonpenetrating solutes is <300 mOsm, the RBC will swell; if it is >300 mOsm, the RBC will shrink.

Problems involving a rapidly penetrating solute

Predict the changes in cell volume (increase, decrease, no change) when a normal RBC previously equilibrated in isotonic saline is placed in the following solutions:

5. 200 mOsm NaCl and 200 mOsm urea
6. 300 mOsm urea only
7. 500 mOsm urea only

Effect of substances that slowly penetrate cell membranes

Some substances penetrate cell membranes but do so slowly. Thus, they initially have an osmotic effect like sodium chloride but no osmotic effect at equilibrium.

Problem involving a slowly penetrating solute

Predict the changes in cell volume (increase, decrease, no change) when a normal RBC previously equilibrated in isotonic saline is then placed in the following solution. Determine the initial effect versus the long-term effect.

8. 200 mOsm NaCl and 200 mOsm glycerol (a slowly penetrating substance)

Answers

1. 200 mOsm NaCl: Because the effective osmolarity of the solution is <300 mOsm, the RBC will swell. Cells in hypotonic saline swell.
2. 400 mOsm NaCl: Because the effective osmolarity of the solution is >300 mOsm, the RBC will shrink. Cells in hypertonic saline shrink.
3. 150 mM NaCl: This is equivalent to 300 mOsm NaCl or isotonic saline. There is no change in RBC volume.
4. 300 mM NaCl: This is equivalent to 600 mOsm NaCl or hypertonic saline. Cells in hypertonic saline shrink.

5. 200 mOsm NaCl and 200 mOsm urea: The effective osmolarity of the solution is determined only by the nonpenetrating solutes. A penetrating substance, such as urea, will diffuse across the membrane and equalize its concentration in the two compartments. Therefore, it will not contribute to effective osmolarity. If the effective osmolarity is less than 300, the cell swells. Here the effective osmolarity is 200; therefore, the cell swells.
6. 300 mOsm urea only: The effective osmolarity of the solution is zero, which is the same as pure water; therefore, the cell swells.
7. 500 mOsm urea only: Again, the effective osmolarity is zero; therefore, the cell swells.
8. 200 mOsm NaCl and 200 mOsm glycerol (a slowly penetrating substance): Timing is important in this question. Initially, the glycerol will not penetrate; therefore, it contributes to the initial effective osmolarity of the solution. Because the initial effective osmolarity is 400, the cell will shrink. With time, the glycerol will penetrate the membrane and equalize its concentration in the two compartments. The long-term effective osmolarity will be due to only the NaCl, 200 mOsm. Therefore, over the long term, the cell will swell.

EDEMA

General Considerations

The edematous state requires two conditions for its development and maintenance:

1. An increase in the Starling forces, which promote the movement of fluid from the vascular compartment to the interstitium
2. Retention of sodium and water by the kidney

In the absence of the renal effect, the development of peripheral edema would be self-limiting, i.e., the movement of fluid from the vasculature to the interstitium would reduce the Starling forces that originally promoted the edema.

Although edematous states do not all develop following the same sequence of events, many follow the path where the Starling forces transfer fluid to the interstitium and the under-filled vascular system is replenished via the rennin-angiotensin-aldosterone system.

Peripheral edema expresses itself in two different forms:

1. Non-pitting edema: This is often referred to as a lymphedema which is a disturbance of the lymphatic system. This can develop after the removal of systemic tissue such as after a mastectomy. Non-pitting edema does not respond to diuretics.
2. Pitting edema: This is the classical, most common type observed clinically. Pitting edema generally responds to diuretic therapy. Common causes include nephrotic syndrome, congestive heart failure, cirrhosis, pregnancy, idiopathic edema, and nutritional edema.

In cirrhosis, it is a combination of portal hypertension due to a rise in intrahepatic vascular resistance and the hypoalbuminemia that are thought to be the main causative agents in the peripheral edema and ascites. Renal retention would then be considered a secondary event.

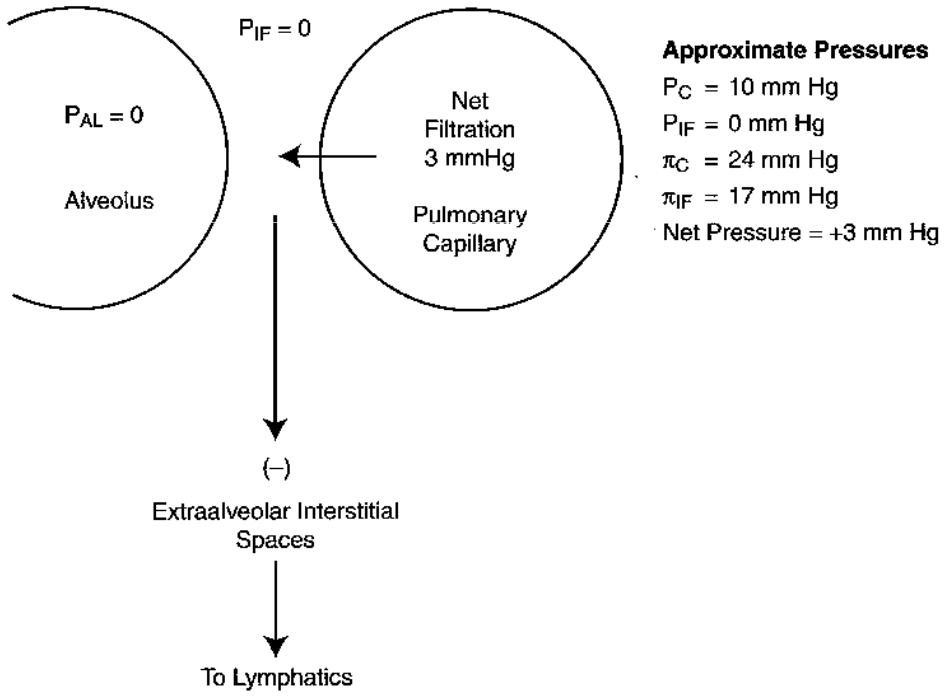
In nephritic edema the decrease in GFR and increased sodium reabsorption may be the primary event. This would differ in nephrotic edema where the primary event is the loss of albumin that exceeds hepatic albumin production.

The preceding points just reemphasize that the etiology may differ but maintenance of the edema involves both the Starling forces and the kidney. The kidney's job is to adjust its excretion of sodium in response to perceived changes in effective circulating volume.

Pulmonary Edema

- Like most tissues, the pulmonary capillary system maintains a small net filtration to the interstitium.
- Unlike most tissues, a second compartment the alveoli must be maintained free of fluid.
- Alveolar space is protected by the alveolar epithelium, which is almost completely impermeable to protein.
- It is the osmotic force of the interstitium that maintains a fluid-free alveolar compartment.

The following represents the forces and fluid movements that normally occur. There will be differences between the lung base and apex as explained in the respiratory section.



P_{AL} = Alveolar Pressure
P_{IF} = Interstitial Pressure
P_C = Capillary Pressure
π_C = Capillary Oncotic Pressure
π_{IF} = Interstitial Oncotic Pressure

Figure I-1-12

Figure I-1-12 shows that in the alveolar region, interstitial and alveolar pressures are both close to zero. However, in the extra-alveolar space interstitial pressure is negative and thus acts as a sink, and the fluid tracts away from the alveoli toward the lymphatics and back into the general circulation. At normal surface tensions they play no role here but if they increase, interstitial pressures decrease and filtration increases.

Almost all pulmonary edemas are due to changes in filtration-reabsorption forces (cardiogenic) or membrane permeability changes (endothelial/alveolar epithelial or non-cardiogenic).

Cardiogenic (pressure-induced, noninflammatory)

- This is the most common form of pulmonary edema.
- Increased left atrial pressure, increases venous pressure, increases capillary pressure, increases filtration.
- Initially increased lymph flow reduces interstitial proteins and is protective.
- First patient sign is dyspnea.
- Lower plasma proteins predispose the patient for cardiogenic edema.
- Pulmonary wedge pressure provides confirmation.
- Sitting upright relieves the pressure-induced edema.
- Treatment is to reduce left atrial pressure, e.g., diuretic therapy.

Non-cardiogenic (permeability-induced, inflammatory)

- This is due to direct injury of the alveolar epithelium or after a primary injury to the capillary endothelium.
- Severe lung injury was originally called adult respiratory distress syndrome (ARDS).
- Most common causes include gastric aspirations and sepsis.
- Fluid accumulation as a result of the loss of epithelial integrity.
- Presence of protein-containing fluid in the alveoli inactivates surfactant.
- Alveolar collapse creates atelectasis, shunting, and hypoxemia (see respiratory section).
- Hyaline membranes, sheets of pink proteinaceous material form in the absence of a functional epithelium.

Chapter Summary

* ECF/ICF fluid distribution is determined by osmotic forces.
* ECF sodium creates most of the ECF osmotic force because it is the most prevalent dissolved substance in the ECF that does not penetrate the cell membrane easily.
* If ECF sodium concentration increases, ICF volume decreases.
* If ECF sodium concentration decreases, ICF volume increases.
* An isotonic environment is about 300 mOsm = 150 mM NaCl.
* Vascular/interstitial fluid distribution is determined by osmotic and hydrostatic forces.
* Osmotic forces across a capillary membrane are determined by proteins.
* The main factor promoting filtration is capillary hydrostatic pressure.
* The main factor promoting reabsorption is the plasma protein osmotic force.
* Edema is the result of altered Starling forces and the renal retention of sodium and water.
* Non-pitting edema results from lymphatic disruption and pitting edema from altered Starling forces.
* Pulmonary edema can be cardiogenic (pressure induced) or non-cardiogenic (permeability induced).

SECTION II

Excitable Tissue

Ionic Equilibrium and Resting Membrane Potential

ELECTROCHEMICAL POTENTIAL

Membrane Conductance

Definition

Membrane conductance refers to the number of channels that are open in a membrane. For example, Na^+ conductance is proportional to the number of open channels that will allow the Na^+ to pass through the membrane. It does not indicate if there will be a net diffusion of ions through the channels.

General properties

If conductance is increasing, channels are opening, and if conductance is decreasing, channels are closing.

The rate at which ions move across a membrane depends on the number of open channels and the net force.

When ions flow through channels, the cell's membrane potential changes. However, under physiologic conditions, too few ions flow to produce a significant effect on the ion's extracellular concentration or the concentration gradient across the membrane.

Channels are classified into three main groups:

- Ungated channels: Because these channels have no gates, they are always open. For example, all cells possess ungated potassium channels. This means there will be a net flux of potassium ions through these channels unless potassium is at equilibrium.
- Voltage-gated channels: In these channels, the gates open and/or close in response to a membrane voltage change. For example, many excitable cells possess voltage-gated sodium channels. The channels are closed under resting conditions, but membrane depolarization causes them to quickly open and then quickly close.
- Ligand-gated channels: The channel complex includes a receptor to a specific substance (ligand). It is the interaction of the ligand with the receptor that regulates the opening and closing of the channel. For example, post-junctional membranes of chemical synapses possess ligand-gated channels, and transmission depends on the interaction of the transmitter and the ligand-gated channel.

Net force

The net force acting on an ion across a membrane is the sum of two independent forces.

Concentration force

This is determined by the concentration difference across the membrane.

The greater the concentration difference, the greater the concentration force.

Electrical force

The size of this force is determined by the electrical difference across the membrane (usually measured in millivolts [mV]). The *in vivo* magnitude is determined by the membrane potential (E_m), which is a value that must be measured or given in a particular example.

The direction of the force is based on the fact that like charges repel and opposite charges attract. For example, if the membrane potential is –70 mV, this represents a force of 70 mV that attracts all positive ions and repels all negative ions.

The Nernst equation

The Nernst equation calculates the electrical force that would prevent diffusion of an ion down its concentration gradient. The concentration of the ion outside the cell and inside the cell are inserted into the equation (ion's concentration gradient or concentration force across the membrane). The calculated number with the appropriate sign is the ion's equilibrium potential. This is what the membrane potential must be for the ion to be at equilibrium. The concentration and electrical forces will be equal and opposite, and there will be no net flux of that ion. If the concentration of the ion changes in the ECF for example, a new equilibrium potential would have to be calculated.

For physiologic conditions, the equation for cations is:

$$E_{X^+} = \frac{60}{Z} \log_{10} \frac{[X^+]_o}{[X^+]_i}$$

E_{X^+} = equilibrium potential
$[X^+]_o$ = concentration outside (extracellular)
$[X^+]_i$ = concentration inside (intracellular)
Z = value of the charge (ignoring sign)

In summary, the main function of the Nernst equation is to calculate the ion's equilibrium potential at a given concentration gradient. The equilibrium potential is the theoretical intracellular electrical potential that would be equal in magnitude but opposite in direction to the concentration force.

Application of the Nernst equation

If the **membrane potential (E_m) has been measured** or given in an example and **the equilibrium potential of an ion (E_x) calculated** by using the Nernst equation, the following conclusions can be drawn:

If E_x equals the measured membrane potential (E_m), the ion is at equilibrium, i.e., the concentration and electrical forces are equal and opposite. If they are not identical, the ion is not at equilibrium, which means if channels in the membrane are open to that ion, there will be a net diffusion of the ion across the membrane.

The difference between E_x and the measured membrane potential (E_m) represents the net force on the ion.

The ion will always diffuse in a direction that brings the membrane potential (E_m) toward its E_x.

The **rate** at which an ion will diffuse across a membrane is directly proportional to the net force and membrane conductance to that particular ion. Note that as an ion diffuses and the membrane potential approaches the equilibrium potential for that ion, the net force on the ion decreases. When the membrane potential reaches the ion's equilibrium potential, the net force is zero.

Consider the following example:

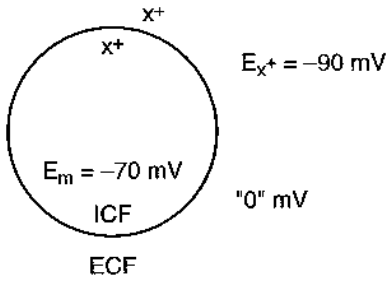


Figure II-1-1

Because the membrane potential is not at –90 mV, the ion is not at equilibrium. If channels in the membrane to x are open, there will be a net diffusion of x across the membrane.

The difference between the membrane potential and the ion's equilibrium potential is 20 mV. This is the net force on the ion.

We know that the positive ion x will flow across the membrane to make the membrane potential approach –90 mV, which means it will become more negative. The only way a positive ion can do that is to flow out of the cell. Thus, when x channels are open, there will be an efflux of x and the membrane potential will move toward –90 mV, assuming no other ions are diffusing in opposition. As the membrane potential gets closer to –90 mV, the net force is decreasing, and if the membrane potential reaches –90 mV, the net force is zero and the net diffusion of x will cease, regardless of the ion's conductance.

RESTING MEMBRANE POTENTIAL

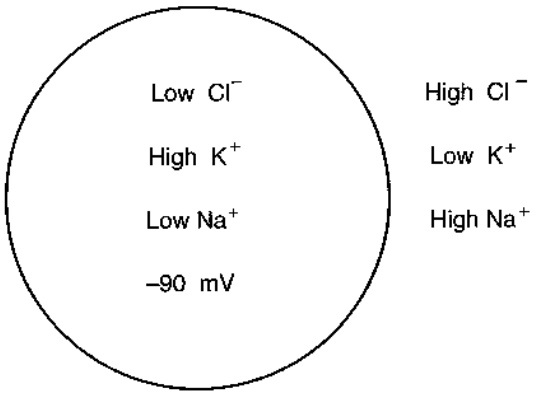


Figure II-1-2

Figure II-1-2 represents a typical cell. If the concentrations of specific ions inside and outside the cell are known, the Nernst equation can be utilized to calculate the equilibrium potential for each ion. Although each cell will be slightly different, assume the following are fairly representative for most cells *in vivo*.

E_{Cl^-} = –90 mV
E_{K^+} = –95 mV
E_{Na^+} = +45 mV

Important Points Regarding Cl^-

Because the measured membrane potential and the calculated equilibrium potential are the same in magnitude and charge, the chloride ions are at equilibrium. No matter what the membrane conductance to chloride is, there will not be a net diffusion of chloride ions, nor will a change in the conductance of chloride in a steady-state situation alter the cell's membrane potential. In many cells, *in vivo* chloride is close to but not at equilibrium.

Important Points Regarding K^+

The potassium ions are not at equilibrium. The net force on the potassium ions is 15 mV. Because this is a small force, the potassium ions can be considered close to but not quite at equilibrium.

Because all cells at all times have open potassium channels (ungated), there must be a net flux of potassium ions across the membrane. Also, because the ion will always diffuse to bring the membrane potential closer to the ion's equilibrium potential, the flux must be an efflux from the cell.

Increasing potassium conductance will accelerate the efflux of potassium ions and hyperpolarize the cell.

Increased extracellular potassium ions will reduce the efflux of the potassium ions or even create an influx of potassium ions, the net result of which will be depolarization.

Decreased extracellular potassium ions will accelerate the efflux of the potassium ions, the net result of which will be hyperpolarization.

Thus, a cell's resting membrane potential is very sensitive to changes in the extracellular potassium ion concentration.

Important Points Regarding Na^+

The sodium ions are not at equilibrium. The net force on the sodium ions is 135 mV. This is considered a large force; therefore, the sodium ions are a long way from equilibrium.

In most cells, including excitable cells under resting conditions, there is not a significant number of open sodium channels (conductance close to zero). Thus, even though there is a large net force, flux is minimal.

An increase in membrane conductance to sodium ions will produce an influx of sodium ions and depolarization.

Because sodium channels are closed under resting conditions, changes in extracellular sodium will not affect the resting membrane potential.

Thus, a cell's resting membrane potential is not sensitive to changes in extracellular sodium.

Pumping Na^+ Out of the Cell

Figure II-1-3 shows the steady-state resting relationship between ion diffusion and the Na/K-ATPase pump.

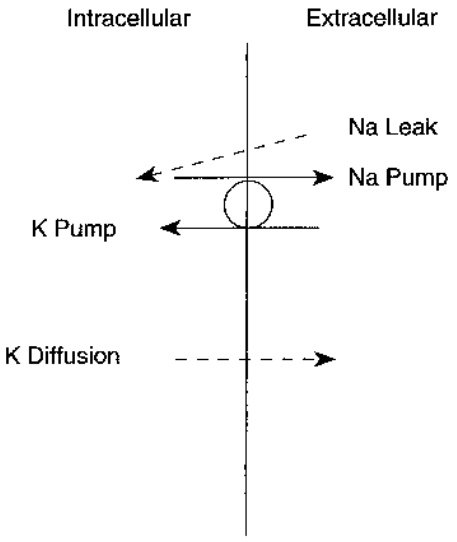


Figure II-1-3

Even though sodium conductance is normally close to zero, the large inward force causes a sodium ion leak. This inward passive leak is balanced by an outward active pumping of sodium ions in exchange for potassium ions. The potassium ions pumped into the cell diffuse out through the ungated potassium channels. If these ungated potassium channels would be suddenly not available, the continued inward pumping of potassium ion would cause a gradual membrane depolarization.

Definitions

Depolarization: The negative intracellular potential moves toward zero (becomes more positive); e.g., Na^+ influx depolarizes a cell.

Hyperpolarization: The negative intracellular potential becomes more negative, e.g., increased K^+ efflux from a cell.

Transmembrane potential: Potential difference across a cell membrane (sign not involved). If the membrane potential is –70 mV, the transmembrane potential is 70 mV. As a cell undergoes depolarization and the membrane potential approaches zero, the transmembrane potential decreases in magnitude.

Chapter Summary

* Membrane conductance indicates whether channels are opened or closed.
* Channels can be classified as ungated, voltage-gated, or ligand-gated.
* The net force on an ion is the sum of the concentration and electrical forces.
* A state of equilibrium represents equal but directionally opposite concentration and electrical forces.
* Equilibrium potential is the electrical potential required inside the cell for an ion to be at equilibrium. It is determined by the ion's charge and its concentration gradient across the membrane.
* Comparing the membrane potential with an ion's equilibrium potential will reveal the net force on the ion, the directional change in the membrane potential as the ion diffuses across the membrane, and whether the diffusion will be an influx or efflux.
* Potassium is close to equilibrium under resting conditions, and because ungated potassium channels are always present, there will be a slow efflux of potassium ions from the cell. A continuous efflux occurs because potassium ions are continuously pumped into the cell.
* The resting membrane potential is very sensitive to the extracellular potassium concentration. Hyperkalemia depolarizes and hypokalemia hyperpolarizes cells.
* Sodium ions are a long way from equilibrium under resting conditions, but because the resting conductance is close to zero, there is very little influx and the resting membrane potential is independent of the extracellular sodium concentration. Even so, there is a slow inward leak of sodium ions. This is countered by the Na/K-ATPase pump.

The Neuron Action Potential and Synaptic Transmission

THE ACTION POTENTIAL

Conduction of nerve signals is done by a rapid membrane depolarization that changes the normal resting negative potential to a positive potential. This is followed by a repolarization back to the normal negative membrane potential. These phenomena define an action potential. Excitable cells, nerves and muscle have action potentials with distinguishing sizes and shapes.

Figure II-2-1 shows the action potential in three types of excitable cells. Even though the following is a description of the neuron action potential, almost identical events occur in skeletal muscle. However, the cardiac ventricular action potential is very different and will be discussed in another chapter.

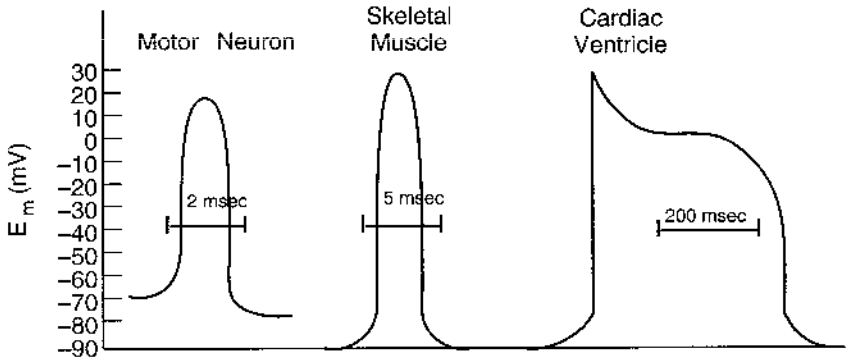


Figure II-2-1. Action Potentials from Three Vertebrate Cell Types (note the different time scales)

(Redrawn from Flickinger, C.J., et al.: Medical Cell Biology, Philadelphia, 1979, W.B. Saunders Co.)

Figure II-2-2 shows the responses of a neuronal membrane to increasing pulses of depolarizing current. When the cell is depolarized to threshold, it fires an action potential. Subthreshold potentials of all types are referred to as *electrotonic* potentials.

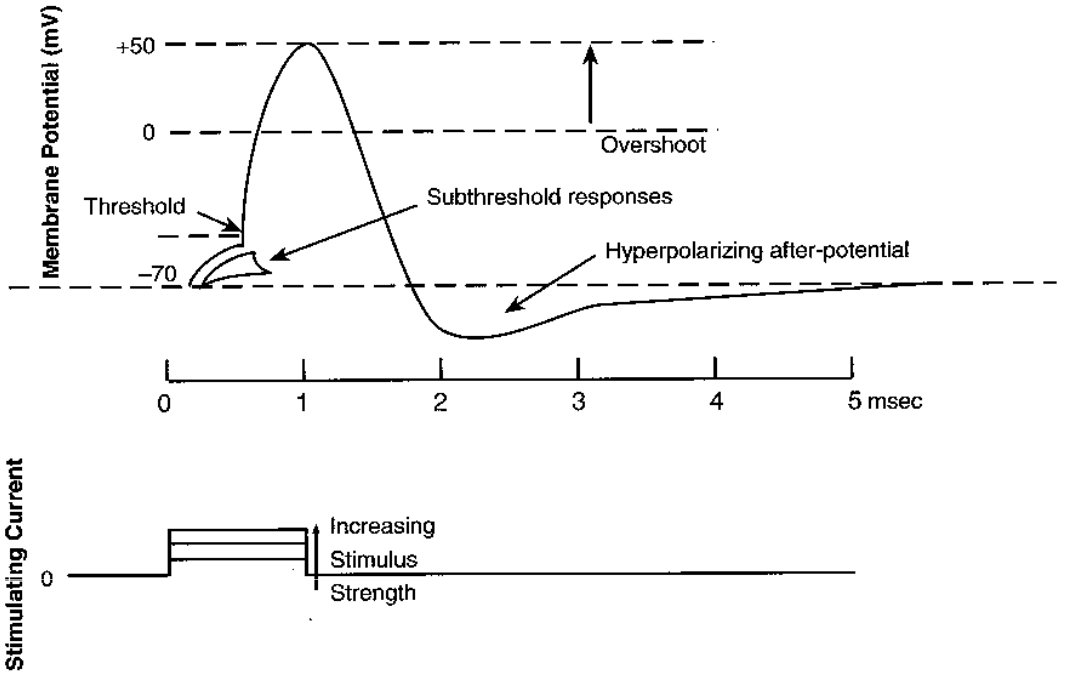


Figure II-2-2. The Neuron Action Potential

Table II-2-1. Subthreshold Potential Change Versus Action Potential

Subthreshold Potential Change	Action Potential
Proportional to stimulus strength (graded)	Independent of stimulus strength (all or none)
Not propagated but decremental with distance	Propagated unchanged in magnitude
Exhibits summation	Summation not possible

MEMBRANE CHANNELS INVOLVED IN THE NEURON ACTION POTENTIAL

Because the action potential is produced by the diffusion of ions through channels, all the resulting events are passive.

Ungated Potassium Channels

These channels are always open, and unless the membrane potential reaches the potassium equilibrium potential (~ –95 mV), a potassium ion efflux is maintained through these channels.

Voltage-Gated Sodium Channels (Fast Na^+ Channel)

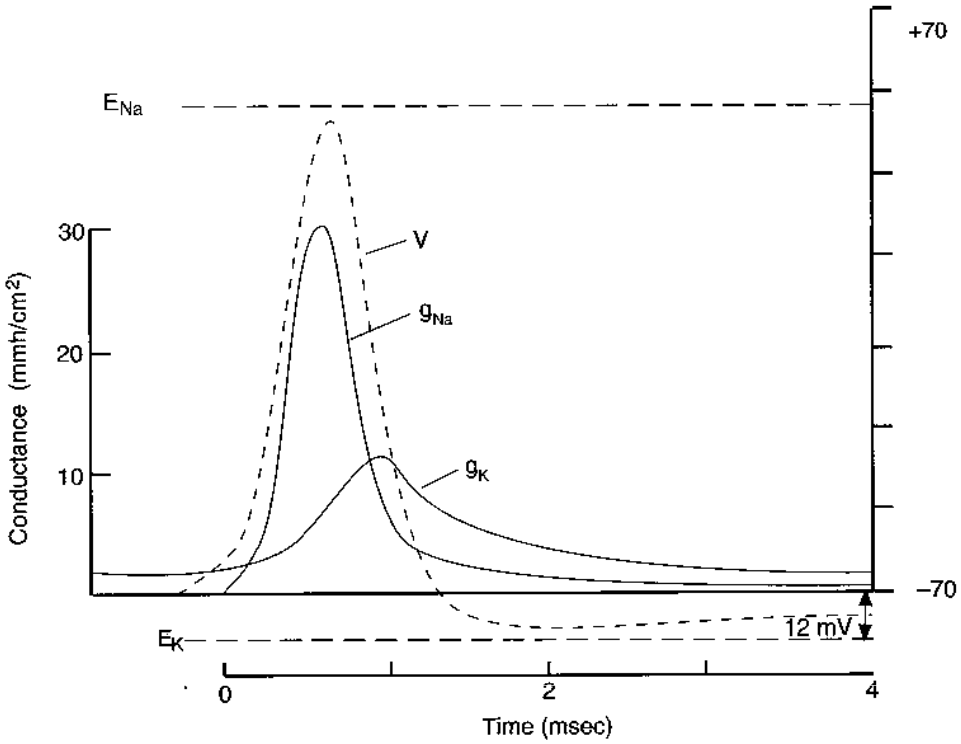
These channels are closed under resting conditions. Membrane depolarization is the signal that causes these channels to quickly open and then close. This time-dependent property is called **inactivation.** Once they close, they will not respond to a second stimulus until the cell almost completely repolarizes. Closure of sodium channels is essential for the rapid repolarization phase of the action potential.

Voltage-gated sodium channels are required for the depolarization phase and thus the generation of an action potential in neurons and skeletal muscle. Preventing the opening of these channels in response to depolarization will prevent the development of an action potential.

Voltage-Gated Potassium Channels

These channels are closed under resting conditions. As is the case for the voltage-gated sodium channel, membrane depolarization is the signal that causes these channels to open. However, they open more slowly than the sodium channels, and thus opening peaks later during the action potential. These channels assist the rapid repolarization phase. Preventing their opening slows repolarization.

Figure II-2-3 shows the conductance changes in sodium and potassium ions in relation to the action potential.



V = membrane potential (action potential)
g_{Na} = sodium ion conductance
g_K = potassium ion conductance

Figure II-2-3. Axon Action Potential and Changes in Conductance

Depolarization Phase

Initial depolarization is the stimulus that causes the opening of the voltage-gated sodium channels (open fast, close fast).

Opening of the sodium channels increases the membrane conductance to sodium ion, permitting a rapid sodium ion influx.

The sodium ion influx depolarizes the membrane close to the sodium equilibrium potential.

Sodium channels are opening throughout depolarization, and peak sodium conductance is not reached until just before the peak of the action potential. Even though peak sodium conductance represents a situation with a large number of open sodium channels, influx is minimal because the membrane potential is close to the sodium ion equilibrium potential.

Repolarization

During early repolarization, the voltage-gated sodium channels are rapidly closing. This eliminates a sodium ion flux across the membrane.

The voltage-gated potassium channels are still opening, increasing potassium conductance beyond the value under resting conditions.

Because at the beginning of repolarization the membrane potential is a long way from potassium ion equilibrium and the membrane conductance to potassium ion is high, there is a rapid potassium ion efflux that repolarizes the cell.

Peak potassium conductance does not occur until about mid-repolarization. At this point, even though the force on the potassium ions is less than at the beginning of repolarization, there is greater efflux because of the much greater conductance.

If the voltage-gated potassium channels do not open during repolarization, the cell will still repolarize due to sodium channel inactivation and through the ungated potassium channels. However, the process will be slower.

The original gradients are reestablished via the (active) Na/K-ATPase pump.

PROPERTIES OF ACTION POTENTIALS

Refractory Periods

Absolute refractory period (functional refractory period)

The absolute refractory period is that period during which no matter how strong the stimulus, it cannot induce a second action potential.

The absolute refractory period is due to voltage inactivation of sodium channels. Also, it is the length of this period that determines the maximum frequency of action potentials. The shorter the absolute refractory period, the greater the maximum frequency.

Relative refractory period

The relative refractory period is that period during which a greater than normal stimulus is required to induce a second action potential.

Figure II-2-4 shows both the absolute and relative refractory periods of the neuron action potential.

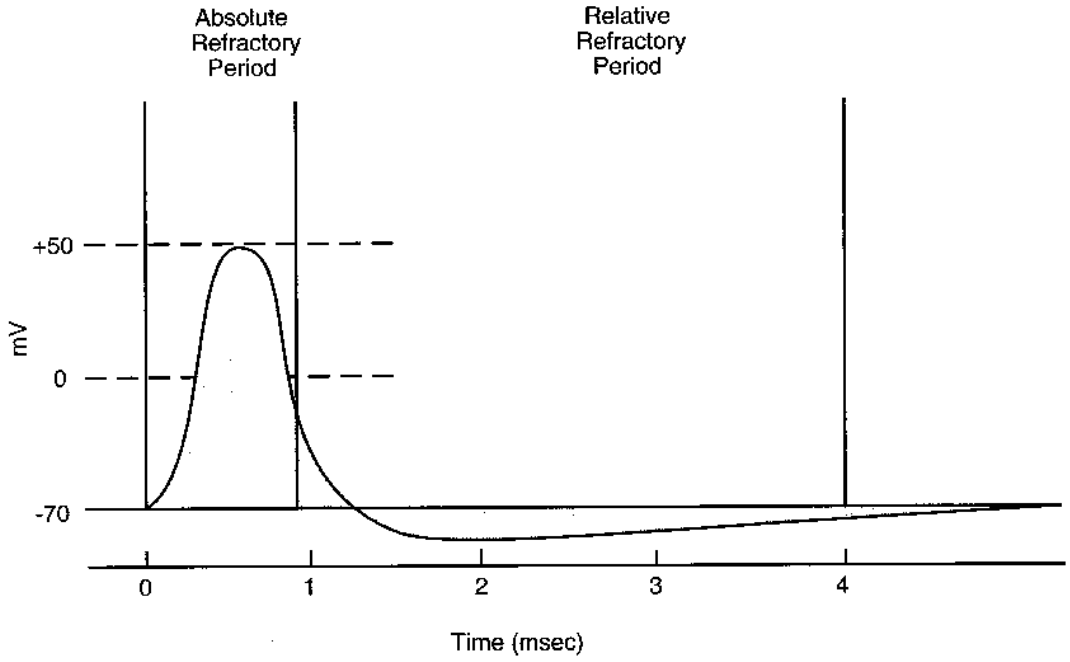


Figure II-2-4. Refractory Periods

Conduction Velocity of the Action Potential

Several factors determine the velocity of the action potential. The following are the most important.

1. Size of the action potential: The greater the size and rate of depolarization of the action potential generated, the faster it moves across the surface of the cell.
2. Cell diameter: The greater the cell diameter, the greater the conduction velocity. A greater cross-sectional surface area reduces the electrical resistance.
3. Myelination: Myelin provides a greater electrical resistance across the cell membrane. The myelination is interrupted at the nodes of Ranvier. With myelin surrounding the membrane, less of the electrical signal is lost during transmission. In other words less current leaks to ground. The signal is conducted with minimal decrement and at greater speed from node to node. It is at the nodes where the sodium and potassium channels are concentrated. The movement of the action potential from node to node is called salutatory conduction.
4. Demyelination (e.g., multiple sclerosis, Guillain-Barre syndrome): This would decrease the amplitude of the action potential as it travels from node to node. If the action potential arrives below a certain magnitude, another action potential may not be generated and transmission is blocked.

NEUROMUSCULAR (CHOLINERGIC) TRANSMISSION

The Neuromuscular Junction

The synapse between the axons of a motor neuron and a skeletal fiber is called the *neuromuscular junction.*

Figure II-2-5 diagrammatically represents the neuromuscular junction.

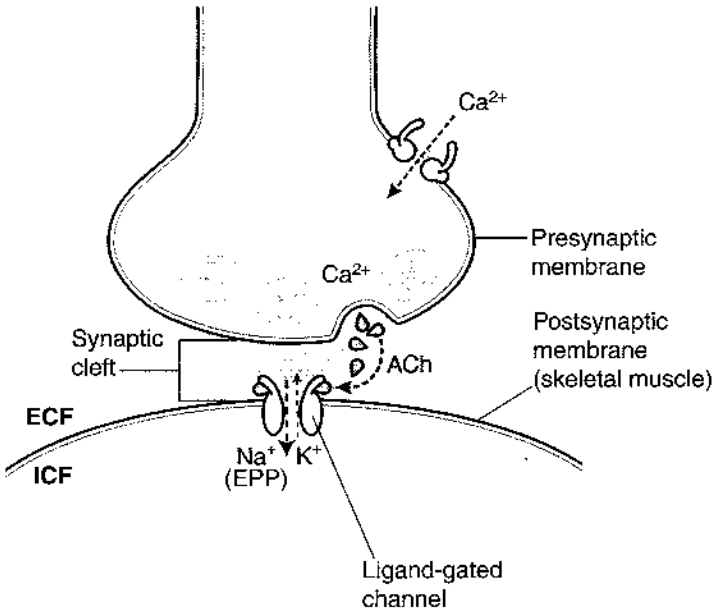


Figure II-2-5. Neuromuscular Transmission and Nicotinic Synapses

Summary of Events Occurring During Neuromuscular Transmission

Action potential travels down the axon, ends in the presynaptic motor axon terminal, and **opens voltage-gated calcium channels.**

↓

Increase in Ca^{2+} permeability of the axon terminal causes **an influx of extracellular Ca^{2+}** into the axon terminal.

↓

The **rise in intracellular free Ca^{2+} causes the release of acetylcholine** from synaptic vesicles into the synaptic cleft.

↓

Diffusion of acetylcholine to the postjunctional membrane, which represents a **major time component that contributes to synaptic delay**.

↓

Combination of acetylcholine with cholinergic, nicotinic receptors on the postjunctional membrane: These receptors are part of a ligand-dependent channel. The channels open when acetylcholine attaches to the receptor, and they remain open until the acetylcholine is removed.

↓

Opening of ligand-dependent channels results in an **increased conductance to Na^+** and K^+. Because of the greater net force on sodium, an influx of sodium dominates.

↓

Influx of Na^+ causes local depolarization of the postjunctional membrane. The magnitude of this depolarization is referred to as the end-plate potential (or EPP). The more acetylcholine that is released, the greater the depolarization (the greater the EPP). Because the skeletal muscle membrane in the synaptic region does not have voltage-gated sodium channels, the action potential cannot be initiated in this region.

↓

The EPP spreads, causing **depolarization of areas of muscle membrane adjacent to the end plate**, where voltage-gated sodium channels are present. Their opening causes the initiation of an action potential that spreads across the surface of the skeletal muscle cell.

Single quanta of acetylcholine are released randomly under resting conditions. Each produces a small depolarization of the postsynaptic membrane, called a miniature end-plate potential (MEPP). MEPPs are subthreshold, so they do not generate action potentials.

SYNAPSES BETWEEN NEURONS

General Features

Figure II-2-6 illustrates synaptic junctions between neurons. The most important aspects associated with synaptic junctions are listed below:

- Synapses are located on the cell body and dendrites.
- The cell membrane in these regions is specialized for chemical sensitivity and thus dominated by ligand-dependent channels, producing excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in response to the different transmitters.
- These voltage changes are conducted electronically along the dendritic and cell body membranes to the axon hillock–initial segment region.
- The closer the synapse is to this region, the greater its influence in determining whether an action potential is generated.
- The axon hillock–initial segment region has a particularly low threshold (voltage gated channels).
- If the sum of all the inputs reaches threshold, an action potential will be generated and conducted along the axon to the nerve terminals.
- Termination of the action of acetylcholine on the postsynaptic membrane is mainly by enzymatic destruction, whereas with other transmitters it is by reuptake by the presynaptic membrane and/or diffusion away from the site of action.

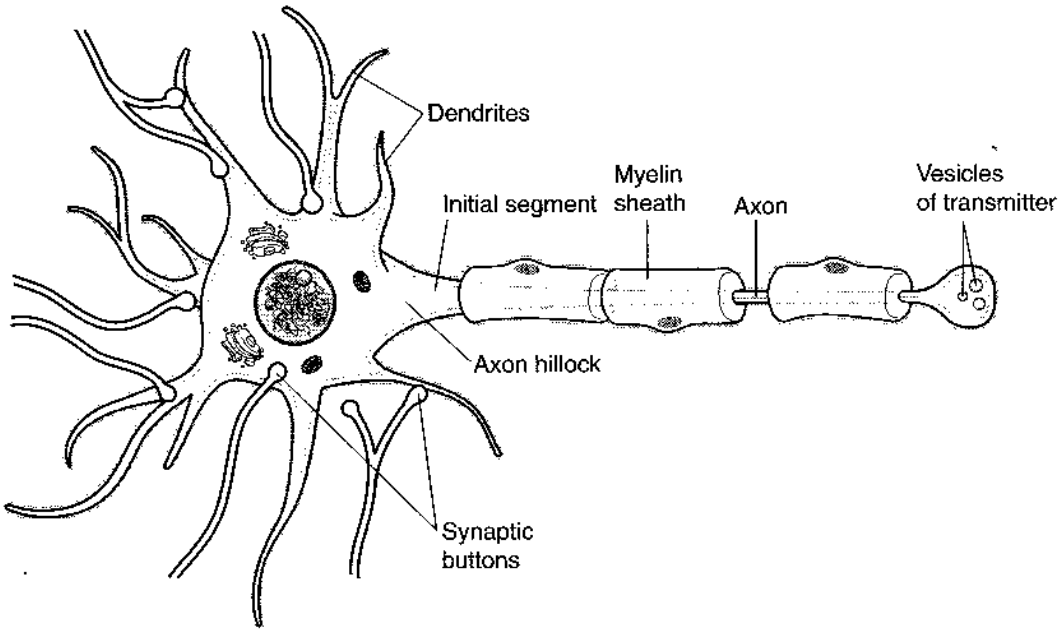


Figure II-2-6. Synapse Transmission between Neurons

Characteristics of EPSPs (Transient Depolarizations)

- They are excitatory because E_m moves closer to its threshold.
- Produced as a result of an increase in conductance to Na^+ and K^+
- The Na^+ influx causes depolarization.
- The EPSPs at synapses between neurons are similar to the EPPs at neuromuscular junctions.
- Transmitters that generate EPSPs would include acetylcholine, glutamate, and aspartate.

Characteristics of IPSPs (Transient Hyperpolarizations)

- They are inhibitory because E_m moves farther away from its threshold.
- Produced at least in some cases by an increased conductance to Cl^-
- The Cl^- influx causes hyperpolarization.
- Transmitters that generate IPSPs would include glycine and GABA.

ELECTRICAL SYNAPSES

- Action potential is transmitted from one cell to another by the direct flow of current.
- Conduction can occur in both directions, and there is essentially no synaptic delay.
- Cells with electrical synapses are joined by gap junctions.
- Cardiac cells and single-unit smooth muscle cells and some neurons have electrical synapses.

Chapter Summary

* The action potential is produced by the simple diffusion of ions through channels.
* Depolarization is via sodium ion influx through voltage-gated channels. These channels are required for neuron and skeletal muscle action potential.
* Maximum sodium conductance is at the peak of the action potential. Because at this point the membrane potential is close to sodium equilibrium, there is little influx of sodium. Repolarization is via potassium ion efflux, mainly through voltage-gated channels.
* Without the opening of potassium voltage-gated channels, repolarization would be a slow process via the ungated channels.
* The absolute refractory period is due to the unresponsiveness of the voltage-gated sodium channels.
* Velocity of the neuron action potential is determined by its magnitude, the diameter of the neuron, and the level of myelination.
* Synaptic transmission involves the entry of extracellular calcium into the nerve terminal. This then triggers the release of the transmitter.
* The postsynaptic membrane is dominated by ligand-gated channels. In most cases, this allows either an influx of sodium (EPP or EPSP) or an influx of chloride (IPSP).
* Termination of acetylcholine action is mainly by enzymatic destruction, whereas with other transmitters it is by reuptake by the presynaptic membrane and/or diffusion away from the site of action.
* Electrical synapses are bidirectional and faster than chemical synapses, which are unidirectional.

Electrical Activity of the Heart

CHARACTERISTICS OF A RESTING VENTRICULAR MUSCLE CELL

Table II-3-1. Characteristics of a Resting Ventricular Muscle Cell*

	Ion Conc. Out	Conc. In	Equil. Pot.	Permeability
K^+	4	135	−94 mV	high
Na^+	145	10	+70 mV	low
Ca^{2+}	2	10^{-4}	+132 mV	low

*Concentrations in mEq/L

MEMBRANE CHANNELS

Ungated Potassium Channels

Always open and unless the membrane potential reaches the potassium equilibrium potential (~ −94 mV), a potassium flux (efflux) is maintained through these channels.

Voltage-Gated Sodium Channels

- These are closed under resting conditions.
- Membrane depolarization is the signal that causes these channels to quickly open and then close.
- Because they open and close quickly, they are sometimes referred to as fast channels.
- These channels have the same characteristics as the voltage-gated sodium channels in the neuron axon.
- Once closed, they will not respond to a second stimulus until the cell repolarizes.

Voltage-Gated Calcium Channels

- Closed under resting conditions, when the membrane potential is highly negative.
- Depolarization is the signal that causes these channels to open, but they open more slowly than the sodium channels.
- Consequently, they are sometimes called the slow channels. They are also called L-type, for long-acting channels.

- Because they allow sodium as well as calcium to pass, the slow calcium-sodium channel is also appropriate terminology.
- The calcium entering the cell through these channels will participate in contraction and will also be involved in the release of additional calcium from the sarcoplasmic reticulum.
- If the fast channels fail to open, depolarization occurs via the entrance of calcium through these channels. In this situation, the action potential of fast response cells will resemble that of slow response cells.

Voltage-Gated Potassium Channels

There are several types of voltage-gated potassium channels, two of which are most important.

Inward rectifying channels, iK_1

- These get their name from the fact that in some experimental conditions, an inward potassium current can occur.
- Open under resting conditions (negative membrane potentials), depolarization is the signal to close these channels.
- They will be closing during the depolarization phase and will be closed during the main part of the plateau phase.
- They reopen again during repolarization. Thus, potassium conductance is exceptionally high under resting conditions, decreases during depolarization, is at a minimum during the plateau phase, and increases back toward the high resting level during repolarization.
- Low potassium conductance during the plateau phase is extremely important; when the cell is depolarized, there is no potential to hold potassium inside the cell, so there would be excessive loss of potassium from the cell during the plateau.

Delayed rectifying channels, iK

- Control is more like potassium channels in nerves; the iK channel opens with depolarization and closes when the cell is repolarized.
- However, they are very slow to open (delayed). They typically open late in the plateau phase of the action potential to speed repolarization.
- They close very slowly. They remain open into the resting potential and contribute to the extended period of the relative refractory period during resting potential.

ACTION POTENTIAL OF A VENTRICULAR FIBER (FAST RESPONSE)

Fast fibers have functioning fast channels. Depolarization will be rapid and the action potential spreads very quickly across the surface of the cell. Fast fibers include ventricular fibers, atrial fibers, and Purkinje fibers.

Slow fibers lack functioning fast channels. As a consequence, depolarization is slower and the action potential travels more slowly across the surface of the cell. Slow fibers include the SA and AV nodal fibers. Fast fibers can be converted into slow fibers. For example, in ischemic tissue, potassium in the surrounding interstitium rises. The less negative resting membrane potential can convert a normally fast fiber into a slow fiber. Conduction is more likely to be blocked in a slow fiber.

Phases

Figure II-3-1 shows the labeled phases of the ventricular action potential. On the same time scale are the conductance changes in sodium (g_{Na}, fast channels), calcium (g_{Ca}, slow channels), and potassium (g_K, voltage-gated channels).

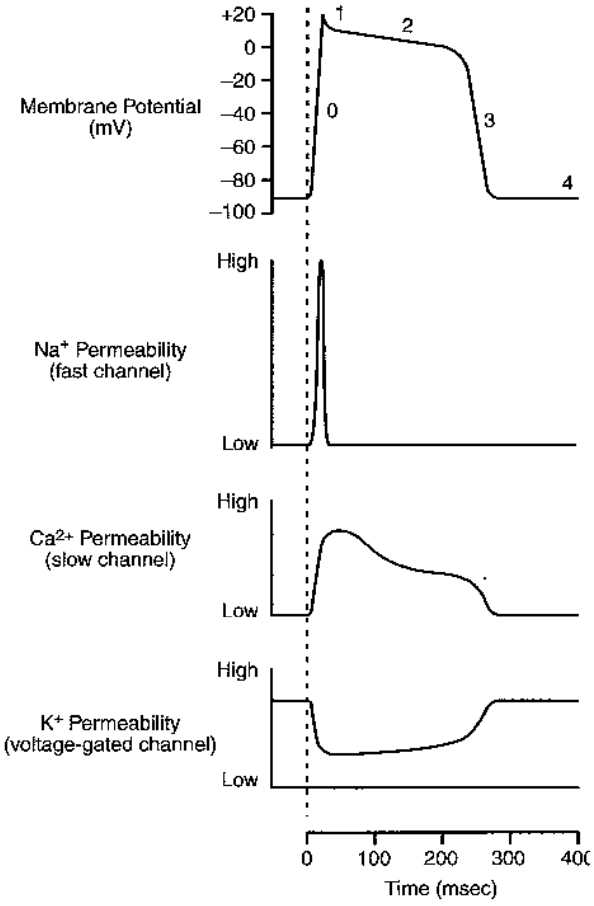


Figure II-3-1. Ventricular Muscle Action Potentia

Ionic Basis of the Action Potential

Phase 0

- Fast channels open, ↑ g_{Na}. Sodium influx then causes depolarization.
- The channels open and close quickly, and they have closed by the time the main part of the plateau phase is entered.

Phase 1

- This slight repolarization is due to a transient potassium current and the closing of the sodium channels. Originally it was thought that Cl was involved, though we now know that is not the case.
- Subendocardial fibers lack a phase 1.

Phase 2

- L-type Ca^{2+} channels are open, gCa ↑ permitting a calcium influx.
- Voltage-gated potassium channels, the iK1, are closed; gK ↓ compared with resting membrane.
- Potassium efflux continues through the ungated potassium channels and possibly other channels.
- If voltage-gated potassium channels did not close during depolarization, early repolarization would occur, preventing the full development of the plateau phase.
- The development of the plateau phase is dependent on the closing of voltage-gated potassium channels.
- Calcium channel antagonists shorten the plateau.
- Potassium channel antagonists lengthen the plateau.

Phase 3

- L-type Ca^{2+} channels close, gCa ↓; this eliminates any influx through these channels.
- Voltage-gated potassium channels, the delayed rectifier iK, then the iK_1 are opening, gK ↑.
- Because we are a long way from the potassium equilibrium potential and conductance to potassium is increasing, a large potassium efflux begins, and the cell quickly repolarizes.
- If the voltage-gated potassium channels did not open, the cell would still repolarize but more slowly, because of closure of calcium channels and potassium efflux through the ungated potassium channels.

Phase 4

- gK high; voltage-gated and ungated potassium channels open. The delayed rectifiers, iK, gradually close but are responsible for the relative refractory period during early phase 4.

ACTION POTENTIAL CHARACTERISTICS OF SPECIALIZED CELLS

General Features

The specialized cells of the heart consist of the cells of the sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje fibers. These cells all possess an unstable phase 4. During phase 4 there is a gradual depolarization to threshold. At that point an action potential is generated.

Characteristics of SA Nodal Cells

Figure II-3-2 shows an action potential of an SA nodal cell.

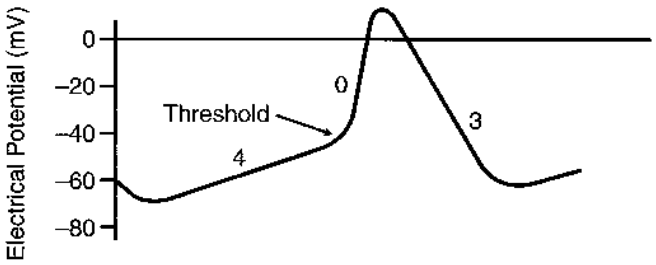


Figure II-3-2. SA Nodal (Pacemaker) Action Potential

General properties

- They all have a pacemaker potential or prepotential.
- Unlike regular contracting myocyte cells, there is not a stable membrane potential during phase 4; rather, there is a slow, gradual depolarization toward threshold.
- Once the threshold is reached, an action potential is generated.
- Also notice that repolarization ends with an initial resting membrane potential that is not as negative as the regular contracting fibers.
- Three factors produce the pacemaker property: a special sodium channel—the i_f, or "funny channel;" a decreasing potassium conductance as the iK channels close; and near the end of the prepotential an increasing calcium conductance (calcium-T channel).

The i_f "funny current"

The funny current is an inward, depolarizing current through a sodium channel that is unlike every other sodium channel. This channel is voltage-dependent, *but it opens when the cell repolarizes and closes when the cell depolarizes.* As phase 3 ends, the funny channel opens and causes sodium influx that reverses the membrane potential and causes the cell to depolarize toward threshold.

Phase 0

Phase 0 is mainly a slow channel (L-type) or calcium spike rather than a fast channel or sodium spike.

Phase 3

As is the case with other action potentials, phase 3 is due to a rapid potassium efflux (gK increases via iK channels).

Effect of sympathetics

The slope of the pacemaker potential increases, threshold is reached sooner, and the intrinsic firing rate increases. Activation of β-adrenergic receptors causes increased "funny current" (sodium), increased calcium current (↑ gCa), and increased potassium current. Figure II-3-3 summarizes the effects of sympathetics on the SA nodal cells.

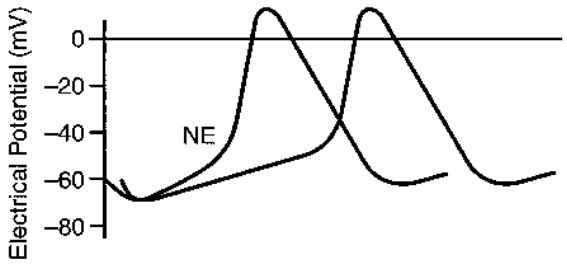


Figure II-3-3. Sympathetic Effects

Effect of parasympathetics

Parasympathetics hyperpolarize the cell via increasing potassium conductance. Thus, it takes longer to reach threshold, and the intrinsic firing rate decreases. There is also a decrease in the slope of the pacemaker potential caused by reduction of the sodium "funny current" and decreased g_{Ca}. Figure II-3-4 summarizes the effects of parasympathetics on the SA nodal cells.

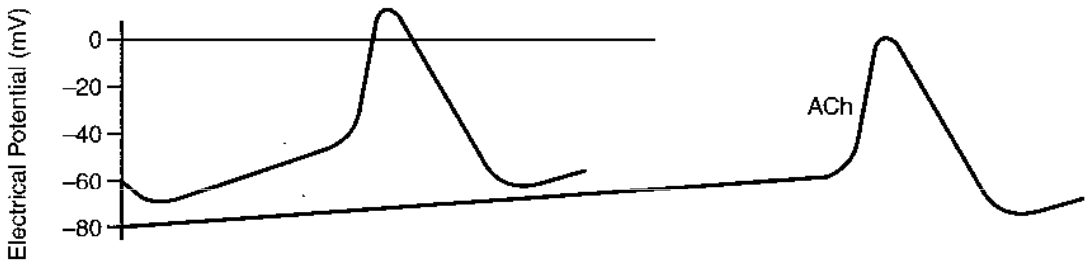


Figure II-3-4. Parasympathetic Effects

Conduction Pathways and Velocity of Conduction

Pathway

- SA node → atrial muscle → AV node (delay) → Purkinje fibers → ventricular muscle

Velocity

- Fastest conducting fiber = Purkinje cell
- Slowest conducting fiber = AV node

Automaticity

- SA nodal cells: Highest intrinsic rate, primary pacemaker of the heart (100–120/min)
- AV nodal cell: Second highest intrinsic rate, secondary pacemaker of the heart (40–60/min)
- Purkinje cells: Slowest intrinsic rate (30–40/min)
- If Purkinje cells fail to establish a rhythm, then ventricular cells may spontaneously depolarize and produce a ventricular beat. However, the frequency is very low and unreliable.

ELECTROCARDIOLOGY

The Electrocardiogram

The normal pattern is demonstrated in Figure II-3-5.

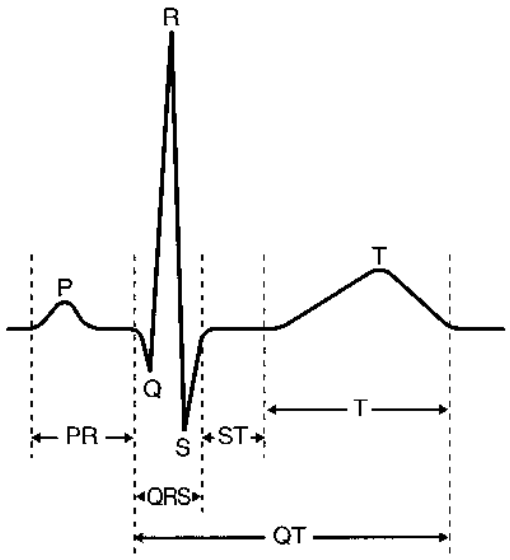


Figure II-3-5. Normal Pattern of an ECG

P wave: Atrial depolarization

QRS complex: Ventricular depolarization

R wave: The first upward deflection of ventricular depolarization is the R wave. In most leads there should not be a prominent Q wave preceding the R wave in the normal heart. A Q wave is any downward deflection of ventricular depolarization that precedes an R wave.

T wave: Ventricular repolarization

PR interval: From the beginning of the P wave to the beginning of the QRS complex (120–210 msec); mostly due to conduction delay in the AV node

QT interval: From the beginning of the QRS complex to the end of the T wave

ST segment: Ventricles are depolarized during this segment. It roughly corresponds to the plateau phase of the action potential.

Important Applications of Intervals

Measurement of intervals

At the standard chart speed of 25 mm/sec, each small division (1 mm) represents 0.04 seconds. An interval of 5 mm would be 0.20 sec, or 200 msec.

PR interval relates to conduction through the atrioventricular node.

QRS duration should be less than 0.12 seconds. Prolonged QRS interval indicates abnormal conduction through the ventricles. There are no pathologies associated with shorter than typical QRS duration.

QT interval indicates ventricular refractoriness. For heart rates between 60 and 100 beats/min, it is usually between 0.35 and 0.44 sec. It varies inversely with heart rate.

ST segment deviation from the isoelectric line may indicate ischemic damage to the myocardium.

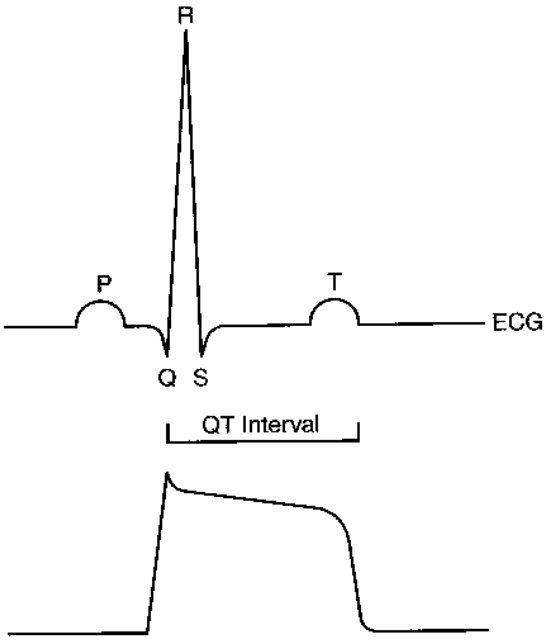


Figure II-3-6. Ventricular Action Potential Versus ECG

Common conventions

- Paper speed: 25 mm/sec
- Calibration: 1 mV = 1 cm pen deflection
- A wave of depolarization approaching a positive electrode leads to an upward deflection of the pen.

Estimation of heart rate

- Two main methods
- Interval method: count the QRS waves within a convenient interval and multiply by the appropriate number to estimate beats/min. For example: 12 QRS waves in 6 seconds = 12 × 10 = 120 beats/min.
- Triplets method: count the number of major divisions (5 mm) between R wave peaks.

  1 = 300 beats/min

  2 = 150

  3 = 100

  4 = 75

  5 = 60

  6 = 50

Both methods are shown in Figure II-3-7.

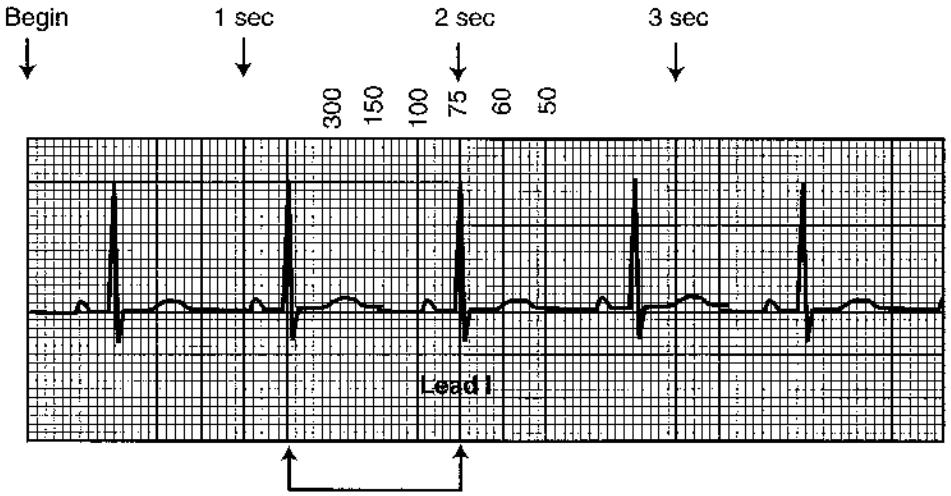


Figure II-3-7. Estimation of Heart Rate

Ventricular depolarization

Proceeds from endocardium to epicardium

Ventricular repolarization

Proceeds from epicardium to endocardium

HEART BLOCK

Partial (First-Degree) Block

- Slowed conduction through the AV node
- PR interval is increased (>200 msec).

Second-Degree Block

Some impulses are not transmitted through the AV node.

- Mobitz I (Wenckebach): PR interval progressively lengthens
- Mobitz II: no measurable lengthening of the PR interval

Figure II-3-8 shows second-degree heart block. This is characterized by some missing QRS complexes following P waves.

Figure II-3-8. Second-Degree AV Nodal Block

Complete (Third-Degree) Block

- No impulses are conducted from the atria to ventricles.
- Atria and ventricles beat independently.
- The electrocardiogram is characterized as having no correlation between P waves and QRS complexes.
- Because of differences in the intrinsic rates of pacemaker tissue, the frequency of P waves is greater than the frequency of QRS complexes.
- Ventricular rate depends upon location of the alternate pacemaker; ventricular origination is slowest and least reliable.
- The low heart rate is associated with a lower than normal cardiac output and syncope.
- Implantation of a pacemaker can alleviate the problems.

Wolff-Parkinson-White Syndrome

- Characterized by the presence of an accessory pathway between the atria and ventricles
- Alterations in the EKG would include: shortened PR interval, widened QRS complex, and slurred upstroke of the R wave (delta wave).
- The cardiac impulse can travel in retrograde fashion to the atria over the accessory pathway and initiate a reentrant tachycardia.

Einthoven's Triangle

Conventional arrangement of electrodes

Figure II-3-9 demonstrates the conventional arrangement of electrodes for recording the electrocardiographic leads and Einthoven's triangle.

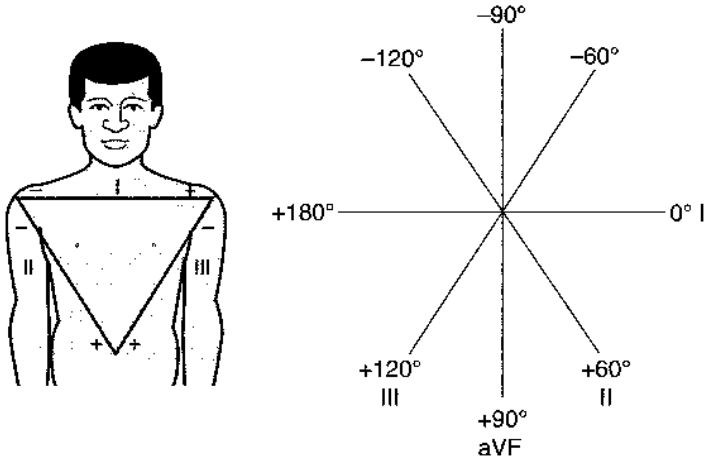


Figure II-3-9. Selected EKG Leads

Einthoven's Law: I + III = II

Mean electrical axis

The mean electrical axis of the ventricles describes the net direction of current movement during ventricular depolarization.

It is affected by a number of factors, including the position of the heart, heart mass, and conduction time. The normal range and deviations are shown in the following figure. Note that although the normal axis is from 0 degrees to +90 degrees, normal variation may be within −30 to +110 degrees, so any value within this range is usually considered normal.

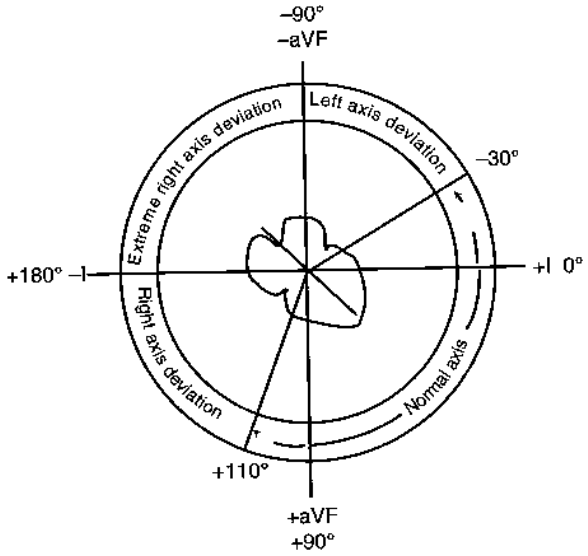


Figure II-3-10. Axis Ranges

Basic Interpretation of Axis Deviations

Left axis deviations are caused by:

- Left heart enlargement, either left ventricular hypertrophy or dilation
- Conduction defects of left ventricle
- Acute MI on right side tends to shift axis left unless right ventricle dilates

Right axis deviations are caused by:

- Right heart enlargement, hypertrophy, or dilation
- Conduction defects of right ventricle
- Acute MI on left side tends to shift axis right unless left ventricle dilates

Chapter Summary

* Fast fibers have fast channels and slow fibers lack fast channels. Inactivation of the fast channels creates a slow fiber. The action potentials of slow fibers are more easily blocked.
* Ventricular depolarization is due to a sodium influx through fast channels. These channels are the same as those that produce depolarization in a neuron and in skeletal muscle.
* The plateau phase is established by a reduced potassium conductance that limits potassium efflux and by an influx of calcium through the slow (L-type) channels.
* Repolarization occurs rapidly because of a large increase in potassium conductance, beginning in the latter part of the plateau phase.
* Specialized cells in the heart are characterized by an unstable phase 4 membrane potential that gradually depolarizes to threshold.
* Phase 0 in an SA nodal cell is due mainly to an influx of calcium through slow (L-type) channels.
* In SA nodal cells, sympathetics increase the slope of the prepotential and thus the intrinsic rate, whereas parasympathetics hyperpolarize and decrease the intrinsic rate.
* First-degree heart block is a slowed conduction through the AV node, second-degree heart block is the lack of transmission of some impulses through the AV node, and third-degree heart block is a total block at the AV node.
* Wolff-Parkinson-White syndrome is characterized by an accessory pathway between the atrium and the ventricles. This causes specific changes on the EKG and may produce a reentrant tachycardia.
* The mean electrical axis of the heart is about 60°. It tends to move toward hypertrophied tissue and away from infracted tissue.

SECTION III

Skeletal Muscle

Excitation-Contraction Coupling

SKELETAL MUSCLE STRUCTURE-FUNCTION RELATIONSHIPS

Ultrastructure of a Myofibril

- A muscle is made up of individual cells called muscle fibers.
- Longitudinally within the muscle fibers, there will be bundles of myofibrils. A magnified portion is shown in the figure below.
- A myofibril can be subdivided into individual sarcomeres. A sarcomere is demarked by a Z lines.
- Sarcomeres are composed of thin and thick filaments creating bands as illustrated in the following figure.
- Contraction causes no change in the length of the A band, a shortening of the I band, and a shortening in the H zone (band).

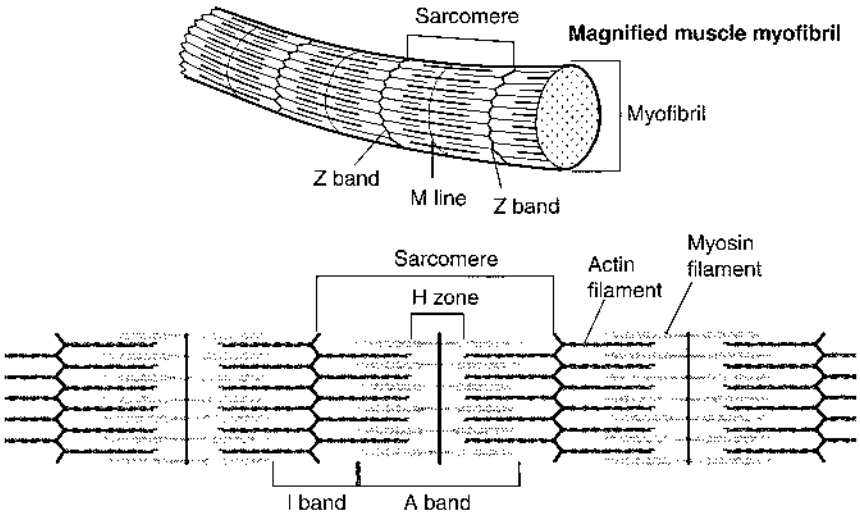


Figure III-1-1. Organization of Sarcomeres

Ultrastructure of the Sarcoplasmic Reticulum

The external and internal membrane system of a skeletal muscle cell is displayed in Figure III-1-2.

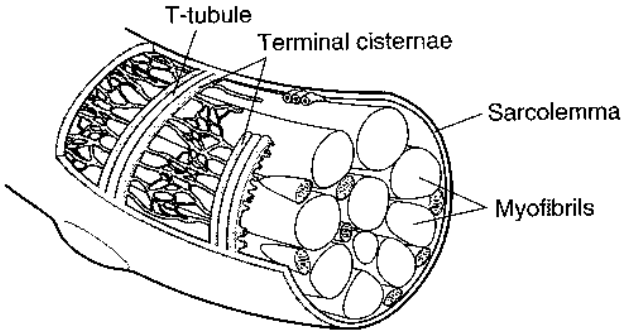


Figure III-1-2. Skeletal Muscle Cell Membranes

The T-tubular membranes are extensions of the surface membrane, and therefore the interiors of the T tubules are part of the extracellular compartment.

The sarcoplasmic reticulum is part of the internal membrane system, one function of which is to store calcium. In skeletal muscle, most of the calcium is stored in the terminal cisternae close to the T-tubular system.

Organization of the Thin and Thick Filaments

Figure III-1-3 shows the relationships among the various proteins that make up the thin and thick filaments and the changes that occur with contraction.

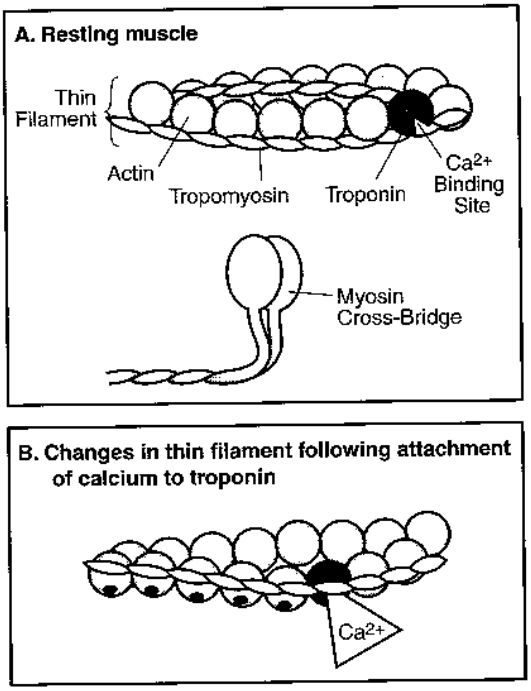


Figure III-1-3. Regulation of Actin by Troponin

Proteins of the thin filaments

Actin

- The structural protein of the thin filament
- Possesses the attachment sites for the cross-bridges

Tropomyosin

- Covers or makes the attachment sites of the cross-bridges unavailable in resting muscle

Troponin

- Composed of three subunits: troponin-T, which binds to tropomyosin; troponin-I, which inhibits myosin binding to actin; and troponin-C, which binds to calcium
- Under resting conditions, no calcium is bound to the troponin, and the attachment sites on the actin are unavailable for cross-linking.
- Early in the contraction process, calcium attaches to the troponin, and it remains attached during cross-bridge cycling.
- When calcium binds to troponin, the troponin-tropomyosin complex moves, making the attachment sites for the cross-bridges on the actin available for cross-linking with myosin cross-bridges.
- Contraction is terminated (cycling is terminated) when calcium is removed from the troponin.

Proteins of the thick filaments

Myosin

Possesses the cross-bridges that can attach to the actin of the thin filaments

- Cross-bridges possess ATPase activity.
- The energy released from the breakdown of ATP on the cross-bridges during contraction is used to power the mechanical aspects of contraction.
- This can be in the form of active tension and/or active shortening of the muscle.

Cross-Bridge Interactions (Chemical-Mechanical Transduction)

Figure III-1-4 illustrates the major steps involved in cross-bridge cycling in a contracting muscle.

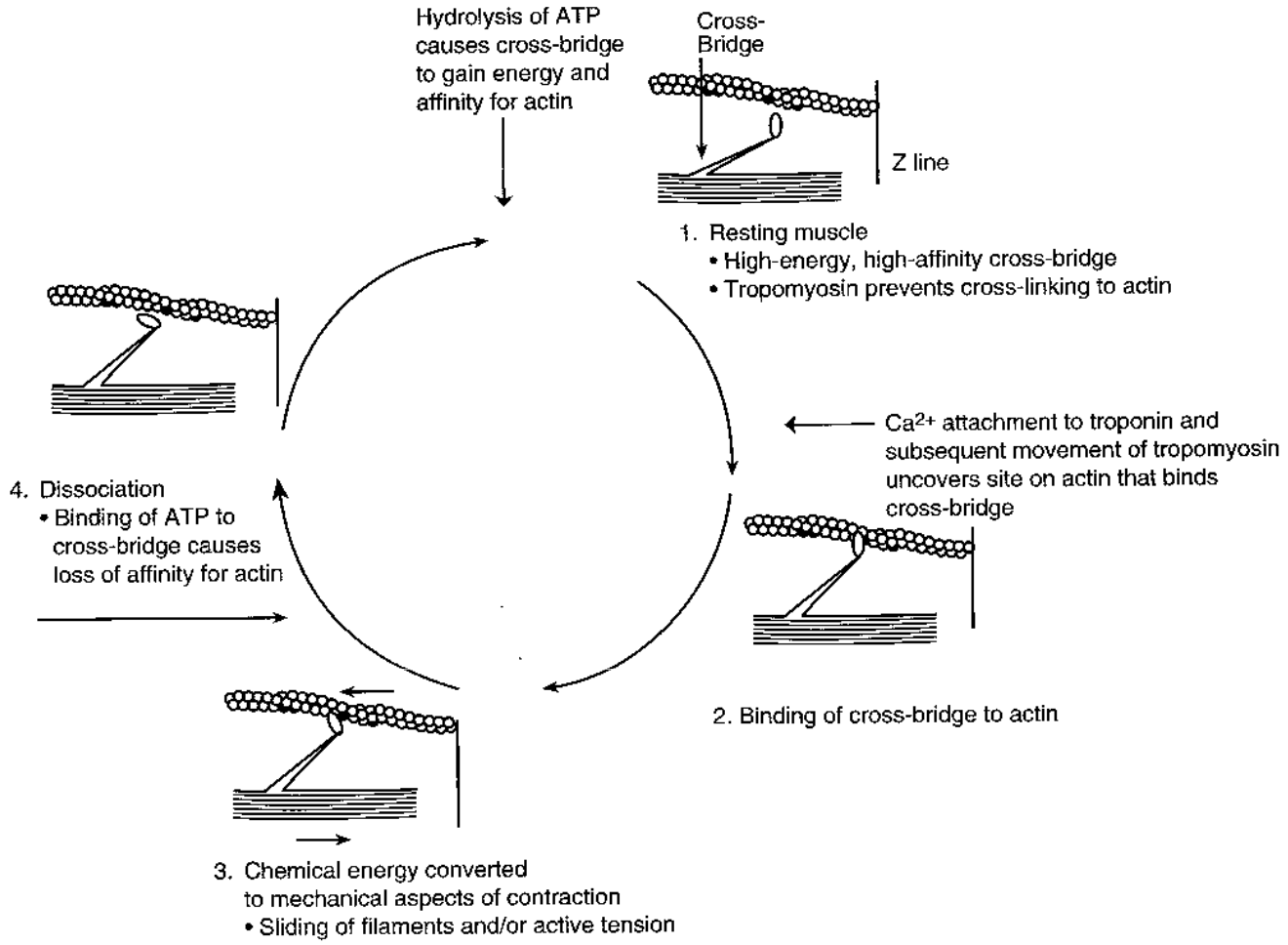


Figure III-1-4. Cross-Bridge Cycling During Contraction

- Cycling starts when free calcium is available and attaches to troponin.
- Contraction is the continuous cycling of cross-bridges.
- ATP is not required to form the cross-bridge linking to actin but is required to break the link with actin.

Every time a cross-bridge completes a single cycle, one ATP is hydrolyzed. This provides the energy for the mechanical aspects of contraction, that is, active shortening and/or the development of active tension.

Cross-bridge cycling continues (contraction continues) until there is either:

Withdrawal of Ca^{2+}: cycling stops at position 1 (normal resting muscle)

or

ATP is depleted: cycling stops at position 3 (rigor mortis). This would not occur under physiologic conditions.

Intracellular Contraction-Relaxation Steps

Sequence

The action potential initiated at the neuromuscular junction travels over the surface of the skeletal muscle cell and down the T tubules, where it terminates. The action potential does not spread across the surface of the sarcoplasmic reticulum, which is an internal membrane system.

↓

Dihydropyridine receptors in the T-tubular membrane are activated. These receptors function as voltage sensors that pull the junctional foot processes away from the ryanodine calcium-release channels in the sarcoplasmic reticulum (Figure III-1-5).

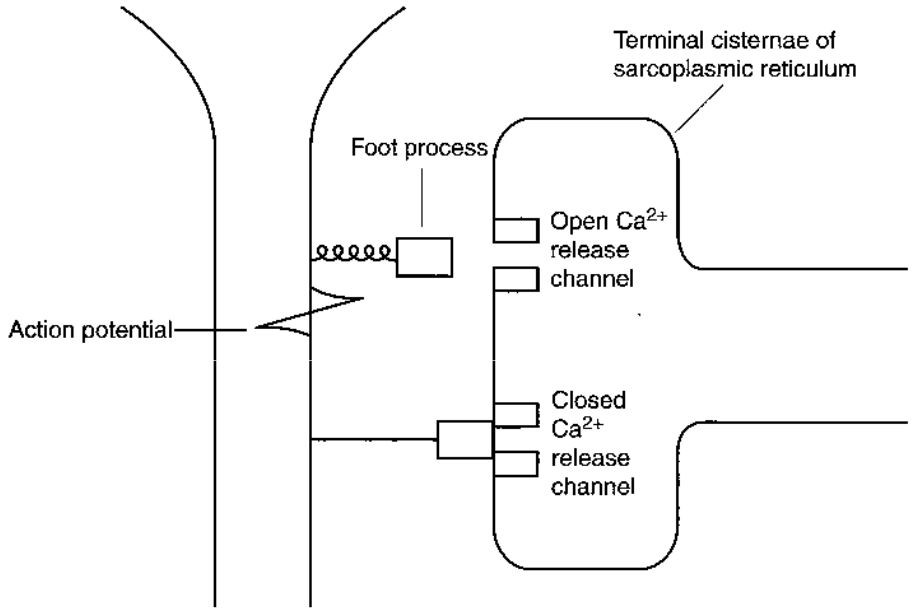


Figure III-1-5. Regulation of Ca^{2+} Release by Sarcoplasmic Reticulum

↓

Calcium, which is stored in the sarcoplasmic reticulum (mainly terminal cisternae), is released into the intracellular environment and diffuses toward the troponin.

↓

Calcium binds to the troponin, causing the tropomyosin to move and expose the attachment sites for the myosin cross-bridges. As long as the calcium remains attached to the troponin, the cross-bridge attachment sites remain available, and cross-bridge cycling continues. The ATP broken down on the cross-bridges produces energy that is utilized for the production of active tension and/or the active shortening of the muscle.

↓

Contraction is terminated (cycling is terminated) by the pumping of the calcium back into its storage depot inside the sarcoplasmic reticulum. This is an energy-dependent active process. This is the normal process of muscle relaxation and ends with the actin and myosin not connected by cross-bridges.

Important points

- Two ATPases are involved in contraction:
  - Myosin ATPase: Supplies the energy for the mechanical aspects of contraction
  - Sarcoplasmic endoplasmic reticulum calcium-dependent ATPase (SERCA): Supplies the energy to terminate contraction
- Therefore, both contraction and the process of relaxation are active events.
- The source of the calcium that binds to the troponin in skeletal muscle is solely from the cell's sarcoplasmic reticulum.
- No extracellular calcium is involved.
- The surface membrane of skeletal muscle does not possess voltage-gated calcium channels (this is not true for cardiac and smooth muscle).

ELECTRICAL VERSUS MECHANICAL EVENTS

Mechanical Response Elicited by Induction of a Single Action Potential

Figure III-1-6 illustrates the mechanical contraction of skeletal muscle and the action potential on the same time scale.

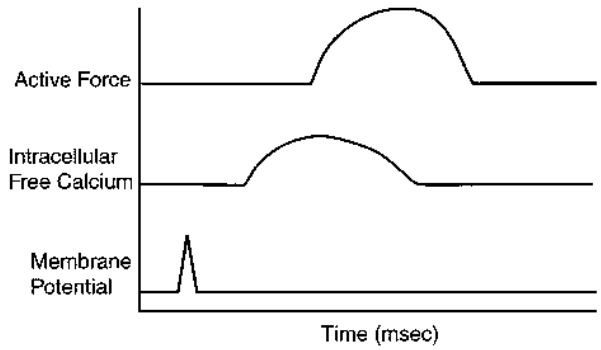


Figure III-1-6. The Time Course of Events During Contraction

Because the electrical event (action potential) precedes the mechanical event and the refractory period has a very short duration, multiple action potentials can occur during the mechanical event.

- Increasing the frequency of action potentials causes the release of more calcium from the sarcoplasmic reticulum and the cycling of more cross-bridges for a longer period of time. This increases the magnitude of the mechanical response. This is summation.
- Complete tetanus is obtained when sufficient free calcium is available for continuous cycling of all available cross-bridges.

Figure III-1-7 shows that cardiac muscle cannot be tetanized because the duration of the effective refractory period (labeled as absolute in Figure III-1-7) is approximately equal to the duration of the mechanical event.

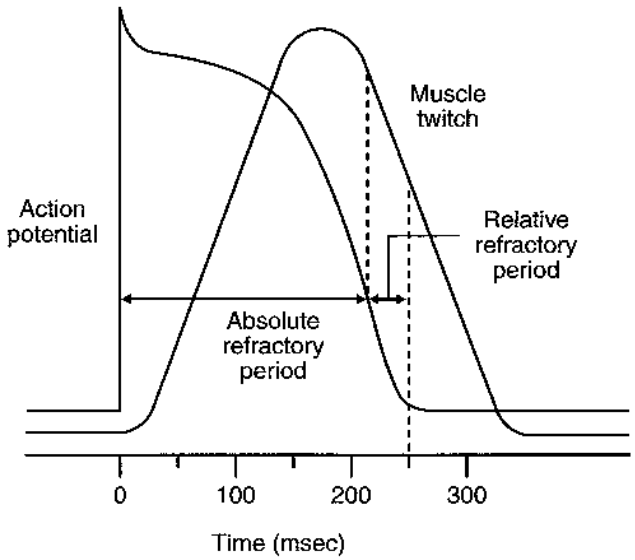


Figure III-1-7. Force and Refractory Periods

Chapter Summary

* Actin is the structural protein of the thin filaments. The regulatory proteins are tropomyosin and troponin, which binds calcium. These proteins determine the availability of cross-linking sites on the thin filaments.
* Contraction is the continuous cycling of cross-bridges.
* The passive release of calcium by the sarcoplasmic reticulum initiates cross-bridge cycling, and its active pumping (calcium-dependent ATPase) back into the sarcoplasmic reticulum terminates cycling.
* The hydrolysis of ATP by the myosin ATPase provides the energy for the mechanical aspects of contraction.
* Saturation of the skeletal muscle cell with free calcium causes tetanus, which is simply the continuous cycling of all available cross-bridges.

Skeletal Muscle Mechanics

PRELOAD AND AFTERLOAD

Preload

Preload is the load on a muscle in a relaxed state, that is, prior to contraction. Applying preload to muscle does two things:

- Causes the muscle to stretch. The greater the preload added, the greater the stretch of the muscle. Along with stretching the muscle, preload stretches the sarcomere. **The greater the preload, the greater the prestretch of the sarcomere.**
- Causes the muscle to develop passive tension. If a 2-g weight is suspended from a muscle, a 2-g force also develops within that muscle. This force is the passive tension. **The greater the preload, the greater the passive tension in the muscle.**

The best measures of preload of any muscle type are those that most directly relate to sarcomere length before the muscle becomes active.

In muscle mechanics, there are two types of tension:

- Passive tension: produced by preload prior to contraction
- Active tension: produced by cross-bridge cycling during the process of contraction

Afterload

Afterload is the force the muscle must develop to shorten and lift the load.

If the muscle must develop a force of 100 lb. to lift a particular load, then the afterload is 100 lb. During contraction, the muscle does not necessarily lift or move the afterload.

LENGTH–TENSION CURVES

Length–tension curves are important in understanding how both skeletal and cardiac muscle function. The graphs that follow are all generated from skeletal muscle *in vitro*, but the information can be applied to both skeletal muscle and heart muscle *in vivo*.

Preload Length–Tension Curve

Figure III-2-1 shows that resting skeletal muscle acts as a simple spring. As preload is added, the muscle stretches and develops a passive tension. The passive tension can be considered an internal force that opposes and equals the preload force.

Preload can be expressed as either length or passive tension; however, because tension can be increased in some circumstances without increasing length, the best measure of preload is length (sarcomere length).

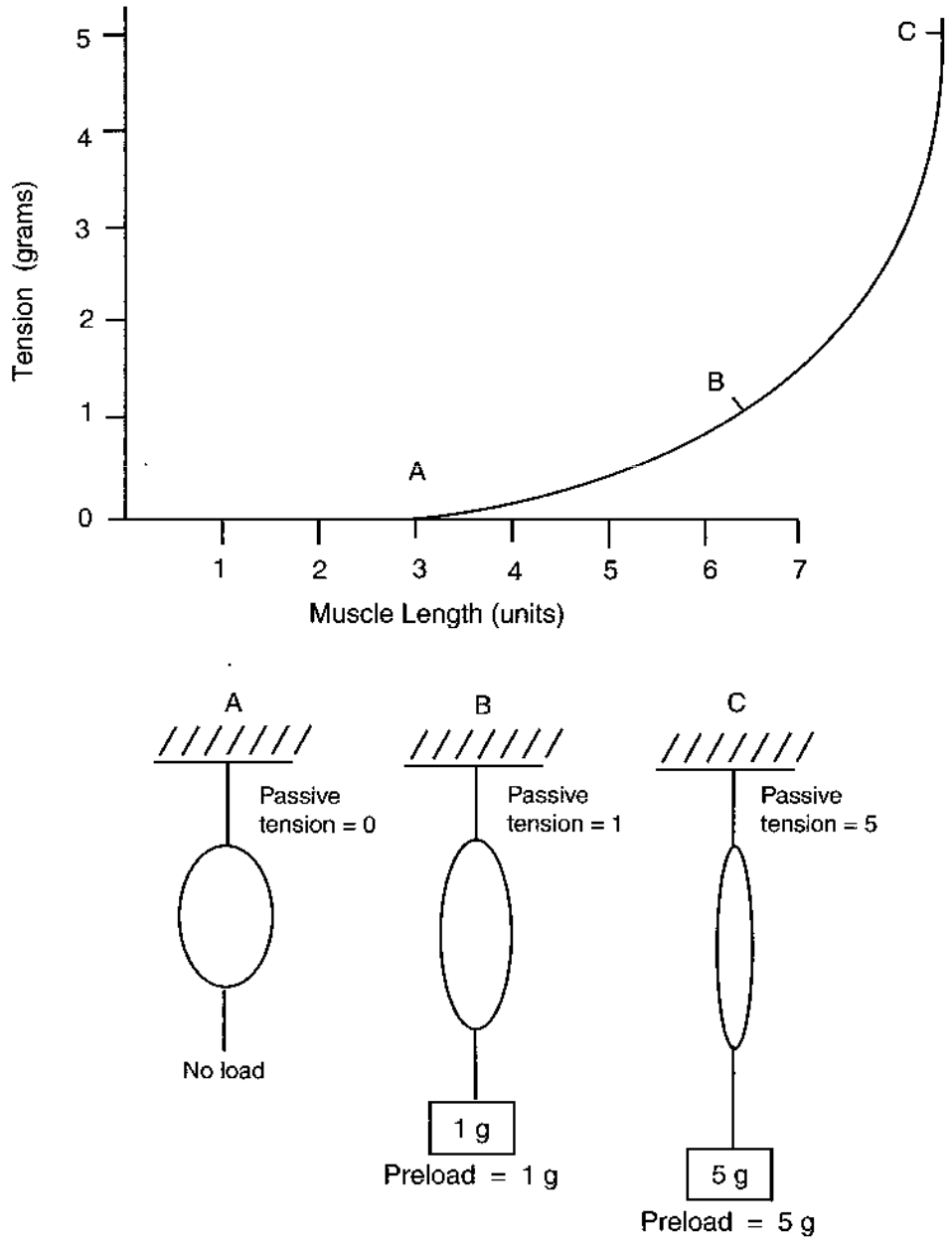


Figure III-2-1. Length, Preload, and Passive Tension

Isometric Tetanic Contraction of the Isolated Skeletal Muscle

During an isometric contraction, the cross-bridge cycling will produce active tension, but the overall muscle length will not change.

The muscle does not shorten and lift the afterload because the afterload is greater than the total tension in the muscle during contraction.

Effect of calcium ion

In a tetanic isometric contraction, the intracellular environment is saturated with free calcium.

- In skeletal muscle, all of the free calcium is from calcium stored in the sarcoplasmic reticulum.
- Under these conditions, all the cross-bridges that can cycle with sites on the actin will be continuously cycling.

Active tension development

The active tension developed during a tetanic isometric contraction is proportional to the number of these cross-bridges that cycle.

- The more cross-bridges that cycle, the greater the developed active tension.

Total tension

The preload creates a passive tension prior to contraction, and cross-bridge cycling during contraction adds an active tension component.

The total tension in the active muscle is the passive or preload tension plus the active tension.

The preceding is illustrated in Figure III-2-2. The numbers presented for both passive and active tension are for illustrative purposes only.

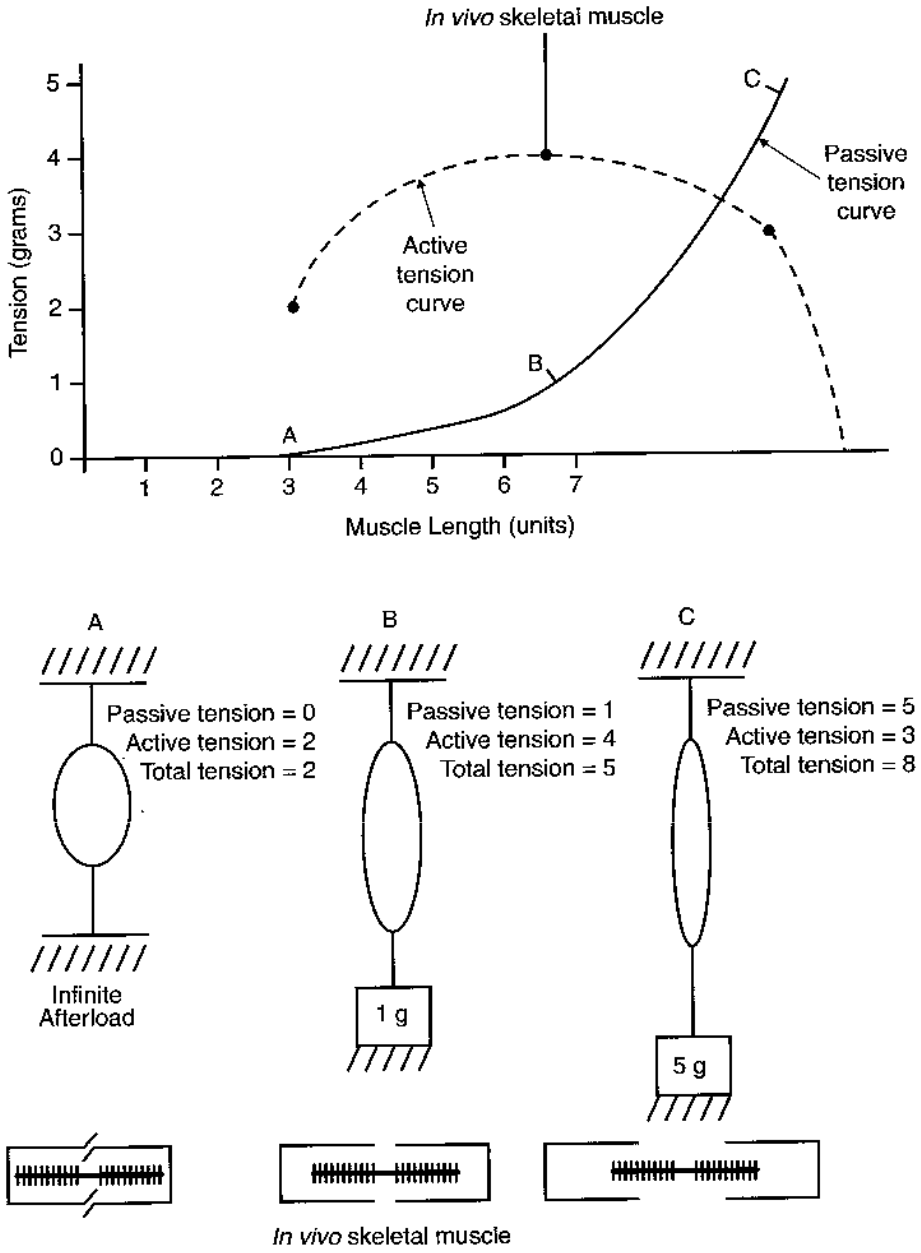


Figure III-2-2. Preload, Active and Passive Tension: The Length–Tension Relationship

RELATIONSHIP BETWEEN VELOCITY AND LOAD

Figure III-2-3 shows that the maximum velocity of shortening (Vmax) occurs when there is no afterload on the muscle. Increasing afterload decreases velocity, and when afterload exceeds the maximum force generated by the muscle, shortening will not occur (isometric contraction).

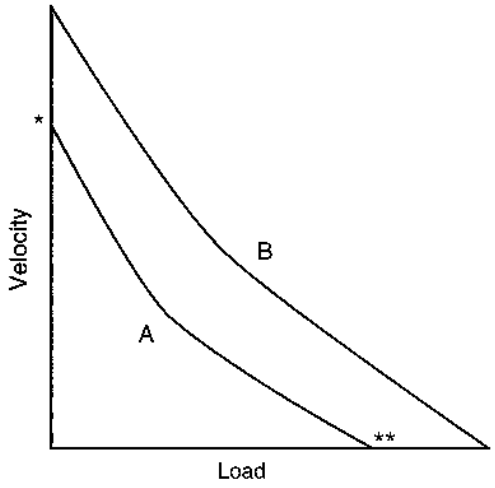


Figure III-2-3. The Force–Velocity Curve

In Figure III-2-3:

*Maximum velocity (Vmax) is determined by the muscle's ATPase activity. It is the ATPase activity that determines a fast versus a slow muscle.

**Maximum force generated by a muscle (or maximum load lifted by a muscle) is determined by muscle mass or, putting it another way, the number of motor units activated during contraction. The greater the muscle mass, the greater the maximum force generated.

Muscle A: a smaller, slower muscle (red muscle)

Muscle B: a larger, faster muscle (white muscle)

As load increases, the distance shortened during a single contraction decreases. So, with increased afterload, both the velocity of contraction and the distance decrease.

PROPERTIES OF WHITE VERSUS RED MUSCLE

White Muscle

Generally, large (powerful) muscle that is utilized short term, e.g., leg muscles of a sprinter, ocular muscles of the eye

Major characteristics

- Large mass per motor unit
- High ATPase activity (fast muscle)
- High capacity for anaerobic glycolysis
- Low myoglobin

Red Muscle

Generally smaller (less powerful) muscle utilized long term (endurance muscle), e.g., postural muscle

Major characteristics

- Small mass per motor unit
- Lower ATPase activity (slower muscle)
- High capacity for aerobic metabolism (mitochondria), which is more efficient than anaerobic glycolysis
- High myoglobin (imparts red color)

FEATURES OF DIFFERENT TYPES OF MUSCLE

Table III-2-1. Histologic Features of Skeletal, Cardiac, and Smooth Muscle

Skeletal	Cardiac	Smooth
Striated	Striated	Nonstriated
Actin and myosin form sarcomeres	Actin and myosin form sarcomeres	Actin and myosin not organized into sarcomeres
Sarcolemma lacks junctional complexes between fibers	Junctional complexes between fibers including gap junctions	Gap junctions
Each fiber innervated	Electrical syncytium	Electrical syncytium
Troponin to bind calcium	Troponin to bind calcium	Calmodulin to bind calcium
High ATPase activity (fast muscle)	Intermediate ATPase activity	Low ATPase activity (slow muscle)
Extensive sarcoplasmic reticulum	Intermediate sarcoplasmic reticulum	Limited sarcoplasmic reticulum
T tubules form triadic contacts with reticulum at A-I junctions	T tubules form dyadic contact with reticulum near Z lines	Lack T tubules, SR controlled by second messengers
Surface membrane lacks calcium channels	Voltage-gated calcium channels	Voltage-gated calcium channels

Chapter Summary

Preload generates passive muscle tension and prestretches the sarcomere.

The amount of sarcomere prestretch determines the maximum number of cycling cross-bridges and thus the maximum active tension.

Skeletal muscle *in vivo* is prestretched to a prelength where potentially every cross-bridge can cycle with actin and contribute active tension.

White muscle is generally large and fast (high ATPase), whereas red muscle is smaller and slower (low ATPase).

Skeletal muscle is fast (high ATPase), each fiber is innervated, and only internally stored calcium is utilized for contraction. This is very different from both cardiac and smooth muscle.

SECTION IV

Cardiac Muscle Mechanics

Cardiac Muscle Mechanics

SYSTOLIC PERFORMANCE OF THE VENTRICLE

General Features

Systolic performance actually means the overall force generated by the ventricular muscle during systole. This is determined by the number of cross-bridges cycling during contraction.

The greater the number of cross-bridges cycling, the greater the force of contraction.

The number of cross-bridges cycling is determined by two independent variables: the amount of preload on the muscle and the level of contractility.

These two factors are summed together to determine the overall force of ventricular contraction. Recent work has demonstrated that they are not completely independent, but the generalizations made here will apply to the physiologic and clinical setting.

Preload

General features

As in skeletal muscle, preload is the load on the muscle in the relaxed state.

More specifically, it is the load or prestretch on ventricular muscle at the end of diastole.

Preload on ventricular muscle is not measured directly; rather, indices are utilized.

The best indices of preload on ventricular muscle are those measured directly in the ventricles.

Indices of left ventricular preload:

- Left ventricular end-diastolic volume (LVEDV)
- Left ventricular end-diastolic pressure (LVEDP)

Possibly somewhat less reliable indices of left ventricular preload are those measured in the venous system.

- Left atrial pressure
- Pulmonary venous pressure
- Pulmonary wedge pressure

Pulmonary wedge pressure, sometimes called pulmonary capillary wedge pressure, is measured from the tip of a Swan-Ganz catheter, which, after passing through the right heart, has been wedged in a small pulmonary artery. The tip is pointing downstream toward the pulmonary capillaries, and the pressure measured at the tip is probably very close to pulmonary capillary pressure. Since the vessel is occluded and assuming minimal flow, the pressure is probably also

very close to left atrial pressure as well. A rise in pulmonary capillary wedge pressure is evidence of an increase in preload on the left ventricle. In some cases, such as in mitral stenosis, it is not a good index of left ventricular preload.

Along similar lines, measurement of systemic central venous pressure would be an index of preload on the right ventricle.

The preload factor in systolic performance (Frank-Starling mechanism)

The preload effect can be explained on the basis of a change in sarcomere length. This is illustrated in Figure IV-1-1.

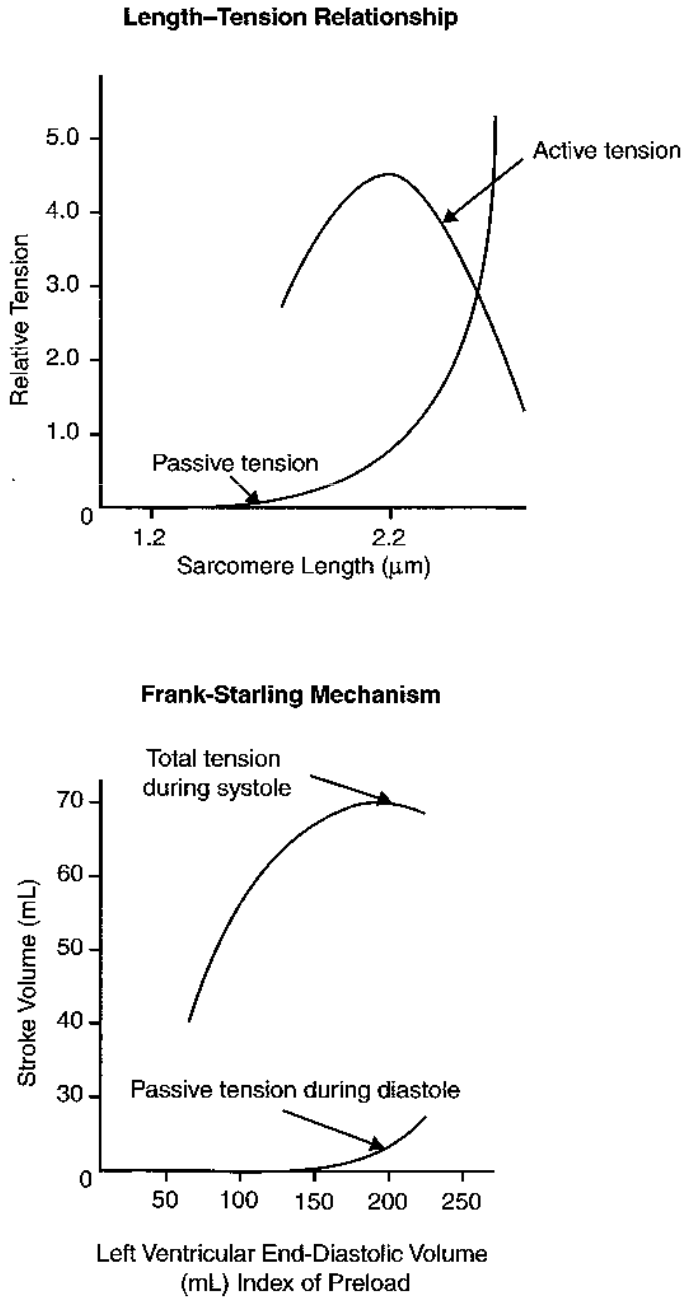


Figure IV-1-1

The resting length of skeletal muscle *in vivo* is at a sarcomere length close to the optimum for maximal cross-bridge linking between actin and myosin during contraction (L_o).

Heart muscle at the end of diastole is below this point. Thus, in a normal heart, increased preload increases sarcomere length toward the optimum actin-myosin overlap. This results in more cross-linking and a more forceful contraction during systole.

Independence of preload and contractility

Figure IV-1-2 and the accompanying description of the graph demonstrate the independence of the preload and contractility factors in acute situations.

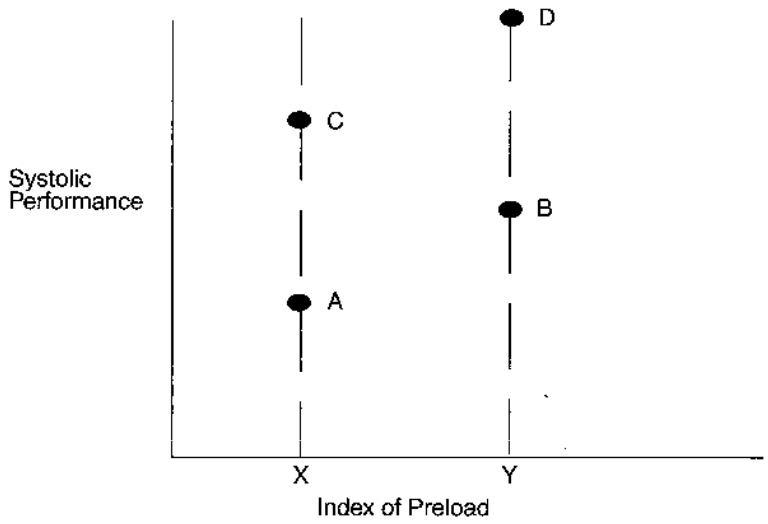


Figure IV-1-2. Preload and Contraction

Assume X represents a normal preload and point A the force generated at this preload under normal resting conditions.

- If preload is increased to point Y, what is observed is an increased force of contraction during systole, point B.
- Thus, we conclude that preload is one factor that determines the overall force of ventricular contraction.
- Further, we can generalize that preload is increased, there will be in most cases an increased force of contraction, whether the heart is normal or diseased.

If we return to our original preload X but in this case simply increase sympathetic activity to the ventricle, we also observe an increased force of contraction, point C, but at the same preload.

- Thus, we must conclude that preload was not responsible for the increased performance and that, therefore, by default, it must have been an increase in contractility.
- This is because there are two factors that determine the overall force of ventricular contraction: preload and contractility.
- It is difficult to define *contractility* without using the word *preload*. For example, a change in contractility can be considered a change in performance at a given preload, or, if a change in performance cannot be explained on the basis of preload, there must have been a change in contractility.

If we increase preload to Y and also increase sympathetic activity, we obtain a very large increase in the force of contraction, point D.

In summary, based on the preceding description:

A → B increased performance due entirely to preload

A → C increased performance due entirely to contractility

A → D increased performance due to an increase in both preload and contractility

The contractility factor in systolic performance (inotropic state)

An acceptable definition of *contractility* would be a change in performance at a given preload.

Thus, contractility is a change in the force of contraction at any given sarcomere length.

Acute changes in contractility are due to changes in the intracellular dynamics of calcium. Drugs that increase contractility usually provide more calcium and at a faster rate to the contractile machinery. More calcium increases the availability of cross-link sites on the actin, increasing cross-linking and the force of contraction during systole. Calcium dynamics do not explain chronic losses in contractility, which in most cases are due to overall myocyte dysfunction.

Indices of contractility

Increased *dp/dt* (change in pressure vs. change in time) = rate of pressure development during isovolumetric contraction. Contractility affects the rate at which the ventricular muscle develops active tension, which is expressed as pressure in the ventricle during isovolumetric contraction.

Increased ejection fraction (stroke volume/end-diastolic volume). Ejection fraction can now be estimated fairly easily by a noninvasive technique and is currently a common clinical index of contractility. There is no ideal index of contractility. Ejection fraction is influenced by afterload, but in most cases an increase in contractility will be accompanied by an increase in ejection fraction. Note that ejection fraction simply indicates the percentage of blood ejected from the ventricle; it does not by itself give information about preload or stroke volume.

When contractility increases, there are changes in addition to an increased force of contraction. This is illustrated in Figure IV-1-3. The solid line represents left ventricular pressure before (and the dashed line after) an increase in contractility via increased sympathetic stimulation. The numbers refer to the descriptions after the figure.

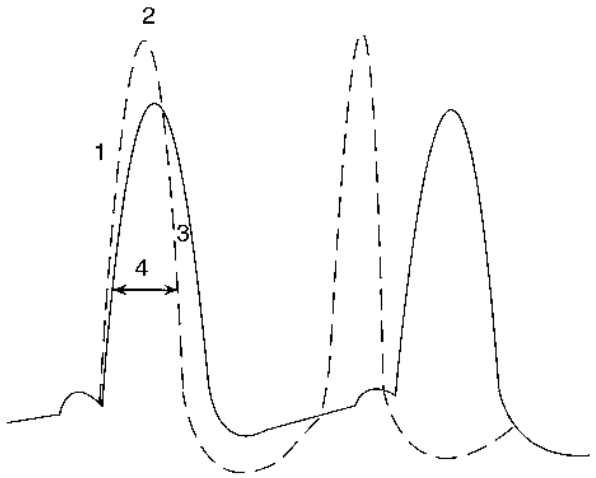


Figure IV-1-3. Effects of Increased Contractility

The overall changes induced by increased contractility can be summarized as follows:

1. Increased *dp/dt*: increased slope, thus increased rate of pressure development
2. Increased peak left ventricular pressure due to a more forceful contraction
3. Increased rate of relaxation due to increased rate of calcium sequestration
4. Decreased systolic interval due to effects #1 and #3

Both an increased preload and an increased contractility will be accompanied by an increased peak left ventricular pressure, but only with an increase in contractility will there be a decrease in the systolic interval.

Whereas contractility affects systolic interval, heart rate determines diastolic interval.

Thus, increased sympathetic activity to the heart will produce the following:

- Systolic interval decreased: contractility effect
- Diastolic interval decreased: heart rate effect

Cardiac Function Curves

Cardiac function curves are an excellent graphical depiction of the effects of preload versus contractility. In Figure IV-1-4, the axes represent the following:

y axis: Index of systolic performance, e.g., stroke work, stroke volume, stroke power (cardiac output). All are indices of the force of ventricular contraction.

x axis: Index of ventricular preload, e.g., ventricular end-diastolic volume or pressure, atrial or venous pressure.

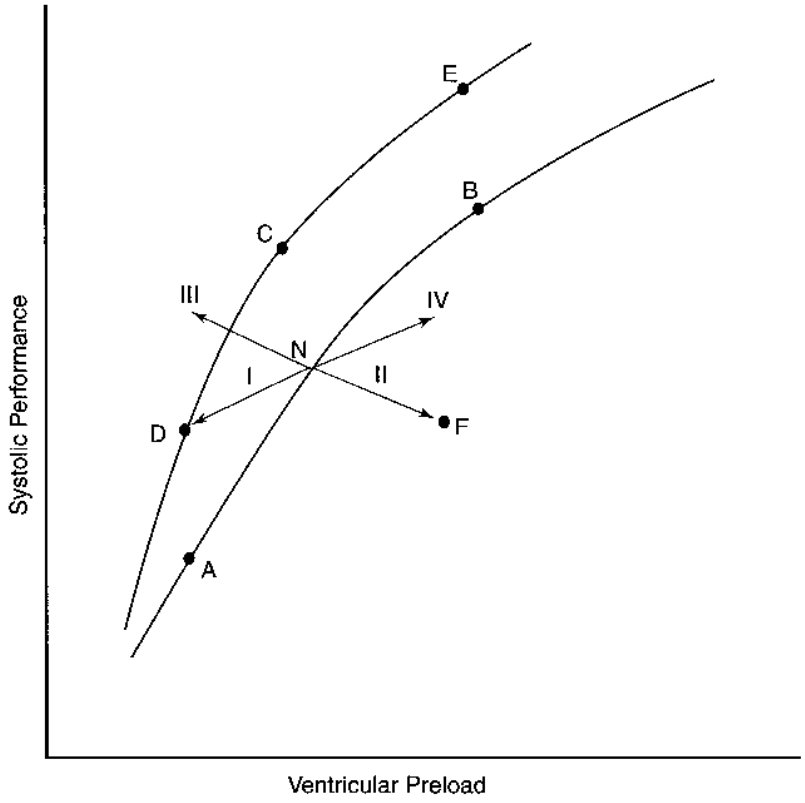


Figure IV-1-4. Cardiac Function Vectors

A cardiac function curve is generated by keeping contractility constant and following ventricular performance as preload increases. Thus:

- All points on a ventricular function curve have the same contractility.
- All curves will have an ascending limb, a peak point, and possibly a descending limb.
- The pericardium normally prevents the large increases in preload necessary to reach the peak of a cardiac function curve.

Starting at N, which represents a normal, resting individual:

- A = decreased performance due to a reduction in preload
- B = increased performance due to an increased preload

Starting at N, point C represents an increased performance due almost entirely to increased contractility (close to the situation during exercise).

- Any point above a ventricular function curve means increased contractility.
- Any point below a ventricular function curve means decreased contractility.

Points C, D, and E represent different levels of performance due to changes in preload only; all three points have the same contractility.

Vector I: consequences of a loss in preload, e.g., hemorrhage

- Performance decreases because of a loss in preload.
- The loss of venous return and preload reduces cardiac output and blood pressure and via the carotid sinus reflex sympathetic stimulation to the heart increases.
- The increased contractility partially compensates for the loss of preload.
- When there is a loss of either preload or contractility that compromises performance, the other factor usually increases to return performance toward normal. However, the compensatory mechanism is usually incomplete.

Vector II: consequences of a loss in contractility, e.g., congestive heart failure

- Performance decreases because of a loss in contractility.
- A decrease in contractility decreases ejection fraction, which increases preload.
- The increased preload partially compensates for the loss of contractility.

Vector III: consequences of an acute increase in contractility

- Performance increases.
- The increased contractility increases ejection fraction.
- The increased ejection fraction decreases preload.

Vector IV: consequences of an acute increase in preload, e.g., volume loading the individual

- The increased venous return increases preload, which increases performance and cardiac output.
- The increased cardiac output would raise blood pressure and via the carotid sinus reflex sympathetic stimulation to the heart decreases.
- The decreased sympathetic stimulation would decrease contractility.

All of the preceding sequences assume no dramatic change in heart rate, which could reduce or eliminate some of the expected changes. Whenever there is a change in sympathetic stimulation to the heart, there should be a change in both contractility and heart rate.

Determinants of Cardiac Output

- Venous parameters, not arterial parameters, normally determine cardiac output.
- Increased resistance of arteries raises blood pressure but does not affect venous return and cardiac output. For instance, aortic stenosis, coarction of the aorta, and hypertension do not decrease cardiac output if the heart if able to pump against the increased afterload.
- Heart rate does not normally affect cardiac output but very low and very high heart rates impede venous return and cardiac output.

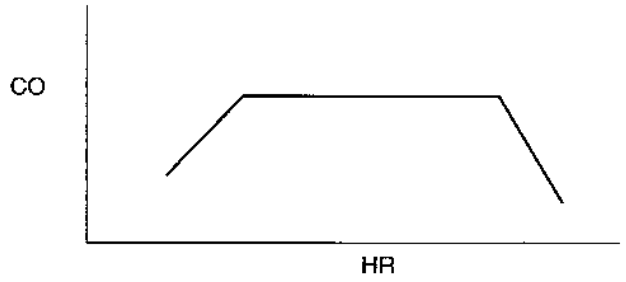


Figure IV-1-5

- Also, ventricular muscle is operating below its pumping capacity, e.g., B blockers that mildly reduce contractility do not reduce cardiac output.
- It is venous return creating a filling pressure and preload that normally determines cardiac output. This is illustrated by overlaying cardiac function and venous return curves (vascular function curves).

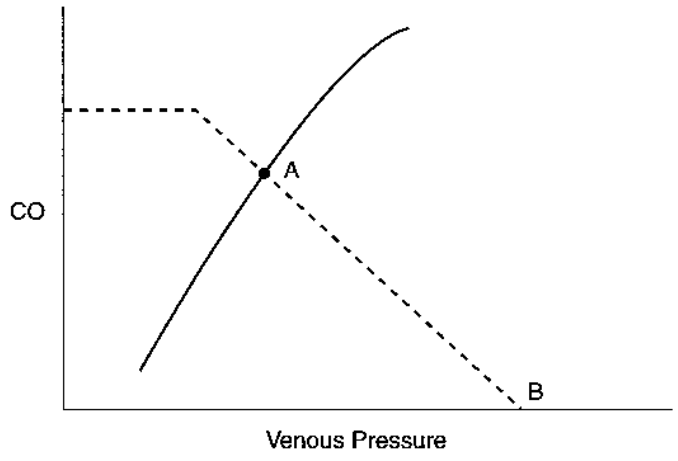


Figure IV-1-6

A = individual operates at the intersection of the cardiac function and venous return curves

B = mean circulatory pressure, which is mainly determined by the volume of blood in the vascular system

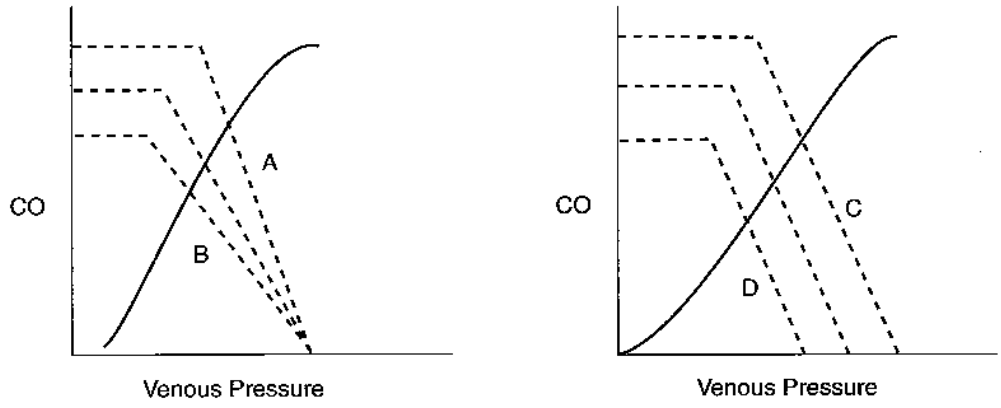


Figure IV-1-7

A = arteriolar dilation
B = arteriolar constriction
C = increased vascular volume
D = decreased vascular volume

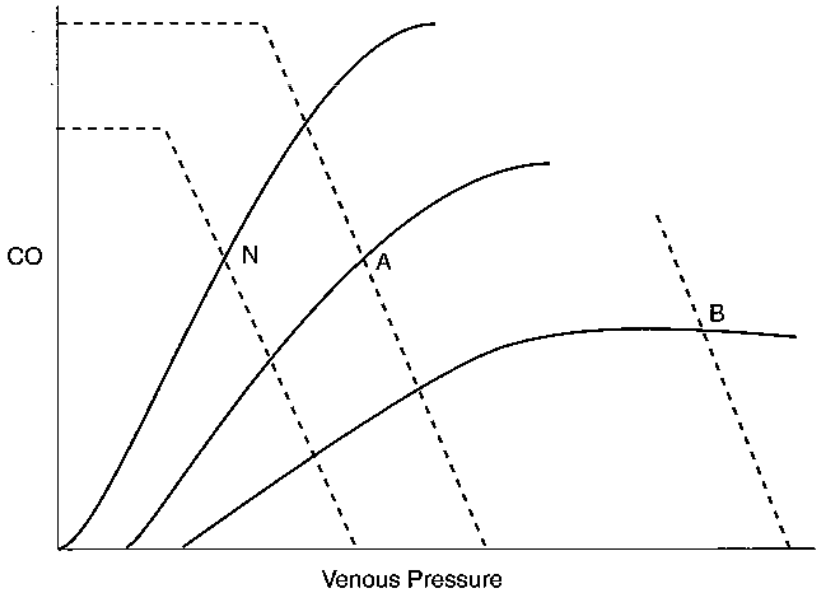


Figure IV-1-8

N = normal operating point
A = compensated failure
B = decompensated failure

In many cases, a combination of diuretics and inotropic agents are given to relieve congestion and return cardiac performance toward normal.

Ventricular Volumes

End-diastolic volume (EDV): Volume of blood in the ventricle at the end of diastole

End-systolic volume (ESV): Volume of blood in the ventricle at the end of systole

Stroke volume (SV): Volume of blood ejected by the ventricle per beat

$$SV = EDV - ESV$$

Afterload

As in skeletal muscle, afterload is the load on the muscle during contraction.

With the left ventricular muscle, it represents the force that the muscle must generate to eject the blood into the aorta. An approximation for the left ventricle is aortic diastolic pressure, which is primarily determined by the resistance of the arterioles (TPR).

Other acceptable indices of afterload on the left ventricle are the following:

Mean aortic pressure

- Hypertension: increased afterload
- Hypotension: decreased afterload

Peak left ventricular pressure

CHRONIC INCREASE IN AFTERLOAD: SYSTOLIC AND DIASTOLIC DYSFUNCTION

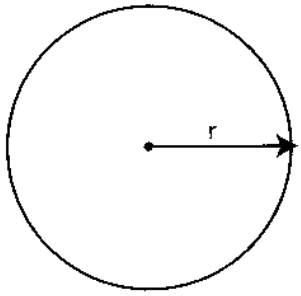
- Systolic dysfunction can be defined as an abnormal reduction in ventricular emptying due to impaired contractility or excessive afterload.
- Diastolic dysfunction is a decrease in ventricular compliance during the filling phase of the cardiac cycle due to either changes in tissue stiffness or impaired ventricular relaxation. The consequence is a diminished Frank-Starling mechanism.
- An increase in afterload can be due to a pressure or a volume overload.

Pressure Overload

- Examples of a pressure overload on the left ventricle would include hypertension and aortic stenosis.
- Initially, there is no decrease in cardiac output or an increase in preload since the cardiac function curve shifts to the left (increased performance due to increased contractility).
- Chronically, in an attempt to normalize wall tension (actually internal wall stress), the ventricle develops a concentric hypertrophy. There is a dramatic increase in wall thickness and a decrease in chamber diameter.
- The consequence of concentric hypertrophy is a decrease in ventricular compliance and diastolic dysfunction, followed eventually by a systolic dysfunction and ventricular failure.

Volume Overload

- Examples of a volume overload on the left ventricle would include mitral and aortic insufficiency, patent ductus arteriosus.
- Fairly well tolerated if developed slowly. A large acute volume overload less well tolerated and can precipitate heart failure.
- Due to the LaPlace relationship, a dilated left ventricle must develop a greater wall tension to produce the same ventricular pressures.



P = T/r
The greater the radius, the greater the wall tension needed to generate the same ventricular pressure.

Figure IV-1-9

- Chronically, in an attempt to normalize wall tension (actually internal wall stress), the ventricle develops an eccentric hypertrophy. This is a modest increase in wall thickness that does not reduce chamber size.
- Compliance of the ventricle is not compromised and diastolic function is maintained.
- Eventual failure is usually a consequence of systolic dysfunction.

Cardiomyopathy

- Cardiac failure or more specifically congestive failure is a syndrome with many etiologies.
- Cardiomyopathy is a failure of the myocardium where the underlying cause originates within the myocyte.
- Excluded would be valvular heart disease, afterload problems, and coronary heart disease
- There are three basic types of cardiomyopathy:
  - Dilated cardiomyopathy
  - Restrictive cardiomyopathy
  - Hypertrophic cardiomyopathy

Dilated cardiomyopathy

- Ventricular dilation with only a modest hypertrophy that is less than appropriate for the degree of dilation
- It can occur for the left heart, right heart, or can include both.
- Diastolic function remains intact and helps compensate for the chamber dilation.
- Compensation also includes increased sympathetic stimulation to the myocardium.
- Systolic dysfunction despite compensations via Frank-Starling and increased contractility
- Further dilation over time and mitral and tricuspid failure enhance systolic dysfunction with eventual complete failure.

Restrictive cardiomyopathy

- Decreased ventricular compliance with diastolic dysfunction and a decrease in ventricular cavity size
- Increased filling pressures lead to left-and-right sided congestion.
- Ventricular hypertrophy may or may not be present.
- Systolic maintained close to normal

Hypertrophic cardiomyopathy

- Septal or left ventricular hypertrophy is unrelated to a pressure overload.
- Diastolic dysfunction due to increased muscle stiffness and impaired relaxation
- Asymmetric hypertrophy of the septum is most common, often resulting in a restriction of the ventricular outflow tract (idiopathic hypertrophic subaortic stenosis) and pulmonary congestion.
- Hypertrophy may be related to septal fiber disarray.

Chapter Summary

* Ventricular performance is determined by the amount of preload and the level of contractility.
* Acutely, the preload effect is determined by sarcomere length, and the contractility effect by the availability of calcium.
* The best indices of preload are ventricular end-diastolic volume and pressure, and indices of contractility include the rate of pressure development during isovolumetric contraction and ejection fraction.
* Both preload and contractility alter the force of ventricular contraction, but only contractility will have a significant effect on systolic interval.
* A loss of preload or contractility will produce an increase in the other factor, which functions to minimize the loss in ventricular performance.
* Venous parameters, not arterial parameters, normally determine cardiac output. It is venous return creating a filling pressure and preload that normally determines cardiac output.
* Afterload on the ventricle represents the overall force the ventricular muscle must develop to pump the blood out of the ventricle. A close approximation for the left ventricle is the pressure it must develop to open the aortic valve. This is aortic diastolic pressure, which is primarily determined by the resistance of the arterioles (TPR).
* Systolic dysfunction is an abnormal reduction in ventricular emptying due to impaired contractility or excessive afterload.
* Diastolic dysfunction is a decrease in muscle compliance and a diminished Frank-Starling mechanism.
* A pressure overloaded ventricle causes a concentric hypertrophy, diastolic dysfunction, and eventually a systolic dysfunction.
* A volume overloaded ventricle causes an eccentric hypertrophy. Diastolic function usually maintained with failure the result of a systolic dysfunction.
* Cardiomyopathy is a failure of the myocardium where the underlying cause originates within the myocyte.

SECTION V

Peripheral Circulation

General Aspects of the Cardiovascular System

GENERAL FEATURES OF THE CARDIOVASCULAR SYSTEM

Organization

Figure V-1-1 illustrates the general organization of the cardiovascular system.

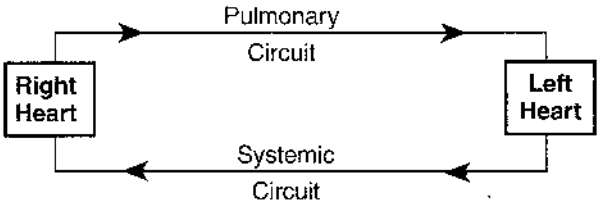


Figure V-1-1. Overview of Circulatory System

The cardiovascular system consists of two pumps (left and right ventricles) and two circuits (pulmonary and systemic) connected in series. When circuits are connected in series, flow must be equal in the two circuits.

Cardiac output is the output of either the left or right ventricle, and because of the series system, they are equal.

Also, the chemical composition of pulmonary venous blood is very close to the chemical composition of systemic arterial blood, and systemic mixed venous blood entering the right atrium has the same composition as pulmonary arterial blood.

Table V-1-1. Pressure Differential

Pressures in the Pulmonary Circulation		Pressures in the Systemic Circulation	
Right ventricle	25/0 mm Hg	Left ventricle	120/0 mm Hg
Pulmonary artery	25/8 mm Hg	Aorta	120/80 mm Hg
Mean pulm. art.	15 mm Hg	Mean art. blood p	93 mm Hg
Capillary	7–9 mm Hg	Capillary: skeletal renal glomerular	30 mm Hg 45–50 mm Hg
Pulmonary venous	5 mm Hg	Peripheral veins	15 mm Hg
Left atrium	5–10 mm Hg	Right atrium (central venous)	0 mm Hg
Pressure gradient	15–5 = 10 mm Hg	Pressure gradient	93–0 = 93 mm Hg

Significant Differences of the Systemic and Pulmonary Circuits

Cardiac output and heart rate of the two circuits are equal, so stroke volumes are the same. Despite this, all pressures are higher in the systemic (peripheral) circuit. This shows that the vessels of the circuits are very different. The systemic circuit has much higher resistance and much lower compliance than the pulmonary circuit. The lower pressures mean that the work of the right ventricle is much lower. In addition, the lower capillary pressure protects against the development of pulmonary edema.

STRUCTURE–FUNCTION RELATIONSHIPS OF THE SYSTEMIC CIRCUIT

General Features

Figure V-1-2 shows that the systemic circuit is a branching circuit. It begins as a large single vessel, the aorta, and branches extensively into progressively smaller vessels until the capillaries are reached. The reverse then takes place in the venous circuit.

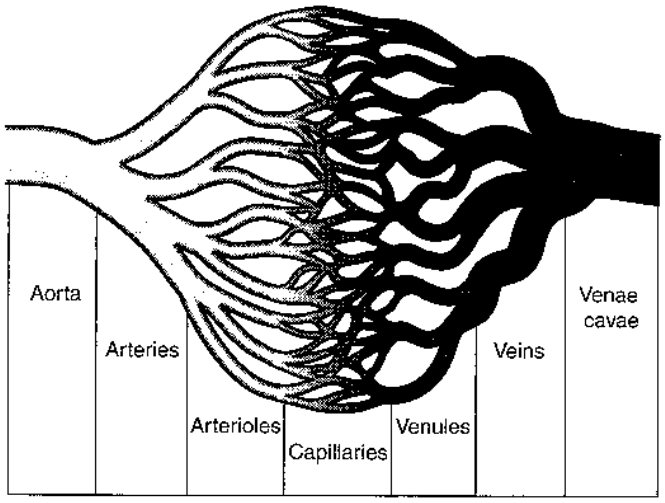


Figure V-1-2. Organization of the Systemic Vessels

Pressures in the Systemic Circuit

Figure V-1-3 shows, in a horizontal subject, the phasic and mean pressures from the aorta to the vena cava.

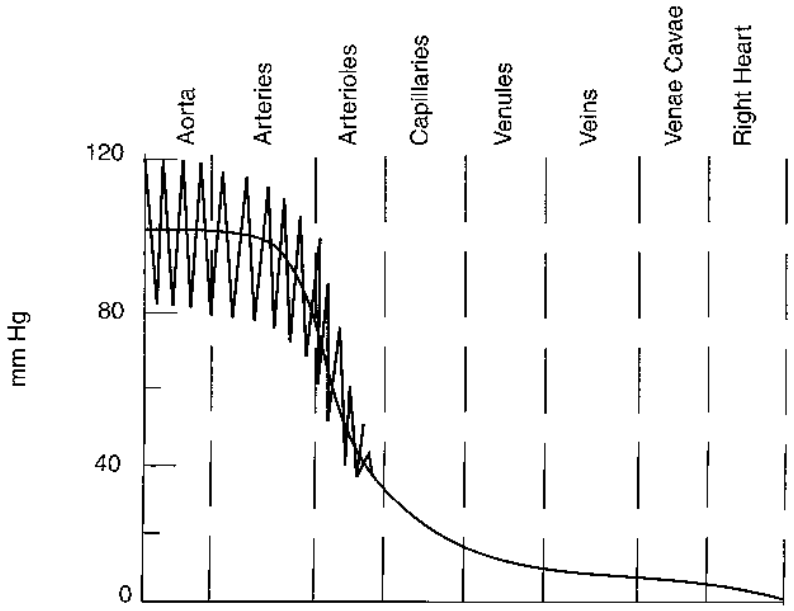


Figure V-1-3. Systemic System Pressures

Pressure in the aorta is normally just below 100 mm Hg (about 93 mm Hg) and decreases toward the right atrium.

The pressure dissipates, overcoming resistance. The amount of pressure lost in a particular segment is proportional to the resistance of that segment.

There is a small pressure drop in the major arteries (low-resistance segment); the largest drop is across the arterioles (highest resistance segment), and another small pressure drop occurs in the major veins (low-resistance segment).

Local arteriolar dilation decreases arteriolar resistance, which increases flow and pressure downstream (more pressure and more flow get downstream).

Likewise, local arteriolar constriction increases arteriolar resistance, and flow and pressure decrease downstream.

Since blood flows from high pressure to low pressure, the sequence of the vessels in any system or part of a system will also be the sequence of pressures, from highest to lowest.

Cross-Sectional Area

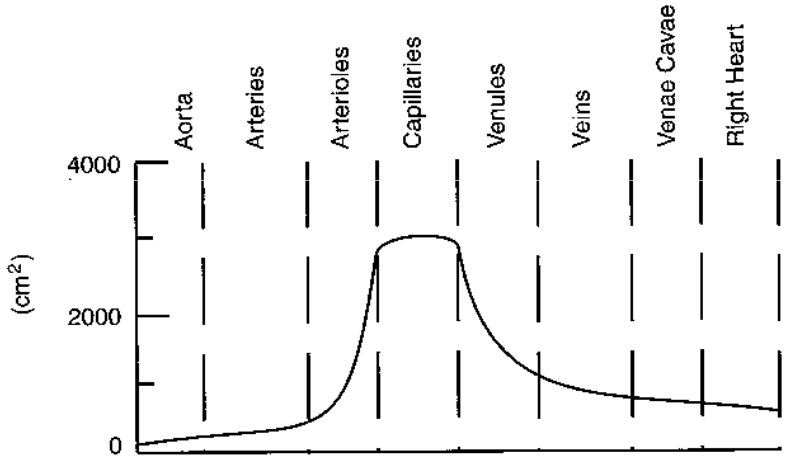


Figure V-1-4. Total Cross-Sectional Areas of Systemic Vessels

- The aorta is a large-diameter vessel, but it is still represents the systemic segment with the smallest cross-sectional area.
- As the aorta branches, the cross-sectional area of each individual vessel decreases, but collectively the cross-sectional area increases to reach a maximum in the capillaries.
- The cross-sectional area then decreases through the venous system.

Velocity

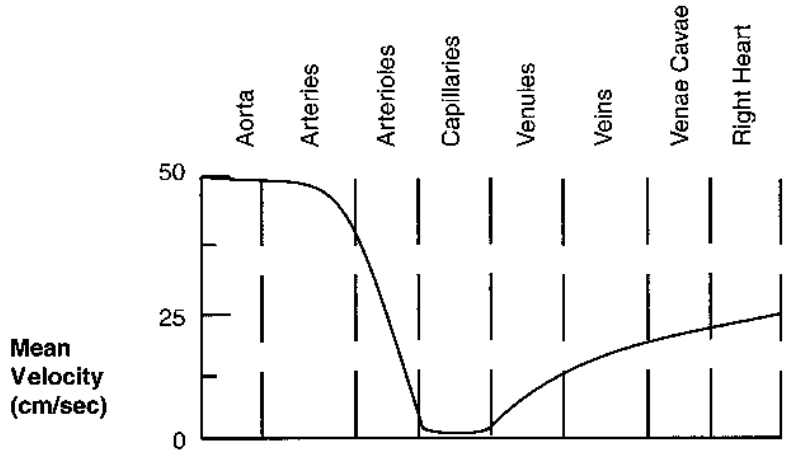


Figure V-1-5. Comparative Velocities in Systemic Vessels

Velocity is inversely related to the total cross-sectional area of all vessels of a particular segment.

Velocity is greatest in the aorta, decreases to a minimum in the capillaries, and then increases from the venules to the right atrium.

Low velocity in the capillaries allows their major function to occur effectively: exchange of dissolved substances between the plasma and the tissues, i.e., **nutritional flow**.

Blood Volume

The largest blood volume in the cardiovascular system is in the systemic veins. The second largest blood volume is in the pulmonary system. Both represent major blood reservoirs.

The systemic veins and the pulmonary vessels have very high compliance compared to the systemic arteries; this is primarily responsible for the distribution of blood volume.

HEMODYNAMICS

Poiseuille Equation

The Poiseuille equation represents the relationship of flow, pressure, and resistance.

The following equation can be applied to a single vessel (Figure V-1-6), an organ, or an entire circuit.

$$Q = \frac{P_1 - P_2}{R}$$

- Q: flow
- P_1: upstream pressure for segment or circuit
- P_2: pressure at the end of the segment or circuit
- R: resistance of vessels between P_1 and P_2

In any vessel the critical value that determines flow is the difference, the **pressure gradient,** between the input (upstream) and output (downstream) pressure, not the input pressure only. An increase of the input pressure that is accompanied by an identical increase of the output pressure will not cause a change of flow; the pressure gradient between input and

output pressure remains the same. This means that an increase in the output (downstream) pressure, for example by a stenosis, reduces the pressure gradient and, therefore, reduces the flow.

Figure V-1-6 illustrates how the Poiseuille equation applies to a single vessel.

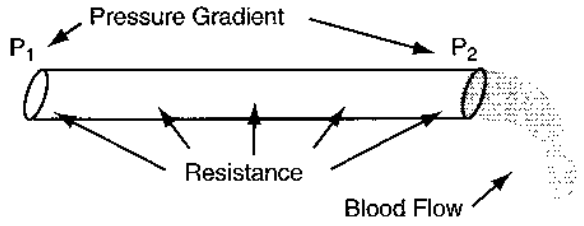


Figure V-1-6. The Poiseuille Equation Applied to Single Vessel

The flow to an organ such as the kidney, for example, could be calculated as mean arterial pressure minus renal venous pressure divided by the resistance of all vessels in the renal circuit.

Determinants of Resistance

$$\text{Resistance} = \frac{P_1 - P_2}{Q} \qquad \text{Units of Resistance} = \frac{\text{mm Hg}}{\text{mL/min}} = \frac{\text{pressure}}{\text{volume/time}}$$

The resistance of a vessel is determined by three major variables: $R \propto \frac{\nu L}{r^4}$

Vessel Radius (r)
The most important factor determining resistance is the radius of the vessel.

- Resistance of a vessel is inversely proportional to the fourth power of the radius.
- If the radius is decreased by half, the resistance increases 16-fold.
- If the radius doubles, the resistance decreases to 1/16 of the original.

Blood Viscosity (ν)
Viscosity is a property of a fluid that is a measure of the fluid's internal resistance to flow:

- The greater the viscosity, the greater the resistance.
- The prime determinant of blood viscosity is the hematocrit.
  Figure V-1-7 shows how viscosity varies with hematocrit.

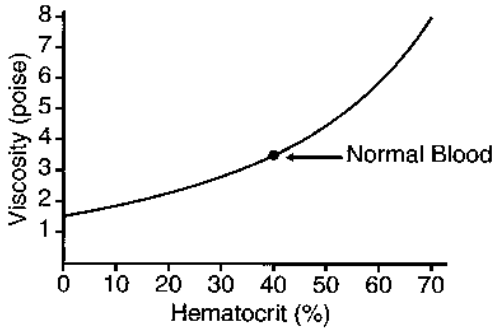


Figure V-1-7. Effect of Hematocrit on Blood Viscosity

Anemia decreases viscosity. Polycythemia increases viscosity.

Vessel Length (L)

The greater the length, the greater the resistance.

- If the length doubles, the resistance doubles.
- If the length decreases by half, the resistance decreases by half.
- Vessel length is constant; therefore, changes in length are not a physiologic factor in regulation of resistance, pressure, or flow. Significant comparisons of different vessels can be made.

Laminar Flow Versus Turbulent Flow

There can be two types of flow in a system: laminar and turbulent.

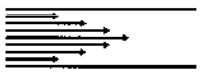


Figure V-1-8. Laminar Flow

Characteristics of laminar flow:

- As shown in Figure V-1-8, laminar flow is flow in layers.
- Laminar flow occurs throughout the normal cardiovascular system, excluding flow in the heart.
- The layer with the highest velocity is in the center of the tube.

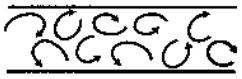


Figure V-1-9. Turbulent Flow

Characteristics of turbulent flow:

As shown in Figure V-1-9, turbulent flow is nonlayered flow.

- It creates murmurs. These are heard as bruits in vessels with severe stenosis.
- It produces more resistance than laminar flow.

Relation of Reynold's number to laminar and turbulent flow

$$\textit{Reynold's number} = \frac{\text{(diameter) (velocity) (density)}}{\text{viscosity}}$$

>2,000 = turbulent flow

<2,000 = laminar flow

The number inducing turbulence is not absolute. For example, atherosclerosis reduces the Reynold's number at which turbulence begins to develop in the systemic arteries. In addition, thrombi are more likely to develop with turbulent flow than in a laminar flow system.

The following promote the development of turbulent flow (i.e., increase Reynolds' number):

- Increasing tube diameter
- Increasing velocity
- Decreasing blood viscosity, e.g., anemia

The vessel in the systemic circuit that is closest to the development of turbulent flow is the aorta. It is a large-diameter vessel with high velocity. This is where turbulence should appear first in anemia.

The following also promote turbulence:

- Vessel branching
- Narrow orifice (severe stenosis)—due to very high velocity of flow

During inspiration and expiration, the conducting airways of the respiratory tree represent mainly a turbulent system. There is high velocity in large tubes with extensive branching.

Series Versus Parallel Circuits

The following represent the consequences of connecting resistors in series.

Figure V-1-10 is a model of three resistors connected in series.

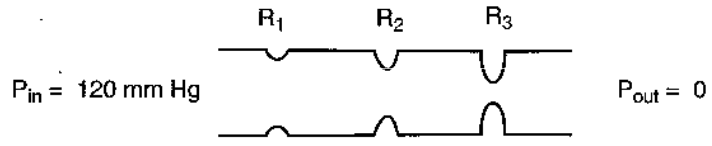


Figure V-1-10. Series Circuit Schematic

A major feature is that flow must be equal at all points in a series system. If the flow changes, it changes equally at all points in a series system.

The total resistance is the sum of the individual resistances:

$$R_T = R_1 + R_2 + R_3 \ldots$$

Therefore, the total is always **greater** than any of the individual resistances.

- Adding a resistor in series increases the resistance of the system.
- Connecting resistors in series results in a high-resistance system.

If P_{in} and P_{out} are kept constant, as in Figure V-1-10, the following will occur if the central resistance (R_2) increases:

- Flow through the series system decreases equally at all points.
- Pressure immediately upstream from R_2 increases toward the perfusing pressure of 120 mm Hg.
- Pressure immediately downstream from R_2 decreases toward 0 mm Hg.

If P_{in} and P_{out} are kept constant, as in Figure V-1-10, the following will occur as the central resistance (R_2) decreases:

- Flow through the series system increases equally at all points.
- Pressure immediately upstream from R_2 decreases.
- Pressure immediately downstream from R_2 increases.

See the "Flow Through a Single Nephron" discussion in the Renal Section (Section VIII) for a practical application of this information.

An important conclusion from the preceding is that the main factor determining capillary pressure is the resistance of the arterioles.

- Decreased arteriolar resistance (dilation) increases capillary pressure
- Increased arteriolar resistance (constriction) decreases capillary pressure

In addition to the preceding events, changes in venous pressure are transmitted upstream to the capillaries.

- Increased venous pressure raises capillary pressure. For example, left heart failure raises left atrial pressure, which raises pulmonary venous pressure, which raises pulmonary capillary pressure.
- Decreased venous pressure lowers capillary pressure. For example, digitalis, which decreases left atrial pressure in congestive heart failure, will reduce pulmonary capillary pressure and relieve congestion. Diuretics will have a similar, often more dramatic effect.

Figure V-1-11 represents a simple model of the systemic circuit.

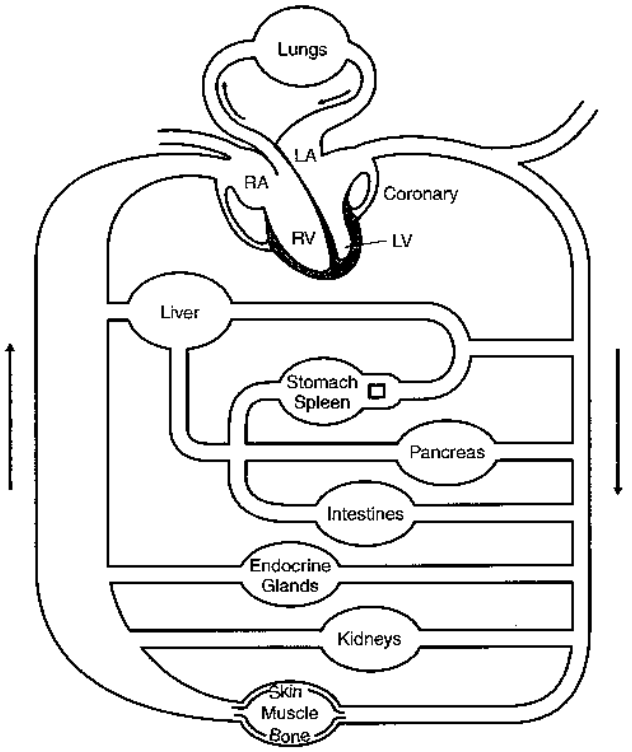


Figure V-1-11. Systemic Circuit

As shown in Figure V-1-11, most systemic organs are connected in parallel. For example, the cerebral, cutaneous, coronary, and renal circuits are all in parallel.

When resistors are connected in parallel, the reciprocal of the total resistance is the sum of the reciprocals of the individual resistances.

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} \cdots$$

If the resistance of each tube is $2 \frac{\text{mm Hg}}{\text{mL/min}}$, then:

$$\frac{1}{R_T} = \frac{1}{2} + \frac{1}{2} + \frac{1}{2} + \frac{1}{2} = 2$$

$$R_T = \frac{1}{2}$$

Therefore:

- Connecting resistors in parallel results in a low-resistance system.
- The total resistance is always **less** than any of the individual resistances.
- Adding a resistance in parallel lowers the resistance of the system.

The addition of parallel circuits (obesity) decreases total peripheral resistance and requires an increase in cardiac output to maintain blood pressure.

The removal of a parallel resistance in the systemic circuit increases total resistance and consequently tends to increase blood pressure. A dramatic example of this occurs at birth (see Fetal Circulation in Section V, Chapter 2).

Also, if blood pressure is kept constant, altering the resistance and thus the flow in one parallel circuit will not change the flow in the remaining parallel circuits.

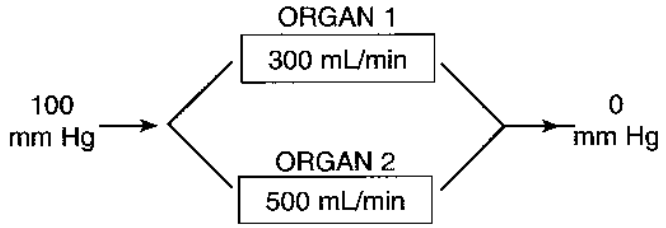


Figure V-1-12. Two Organs Connected in Parallel

- The difference in flow is due to different resistance. Organ 1 has higher resistance.
- When structures are connected in parallel, flows can be independently regulated by changing resistance.
- This is not the case for structures connected in series.

The following are listed from the greatest to least resistance:

- Coronary
- Cerebral
- Renal
- Pulmonary

WALL TENSION

LaPlace relationship:

$T \propto Pr$ T = wall tension
P = pressure
r = radius

The aorta is the artery with the greatest wall tension (greatest pressure and radius).

Development of an Arterial Aneurysm

Figure V-1-13 shows a developing arterial aneurysm. The pressures at points A, B, and C will be approximately the same.

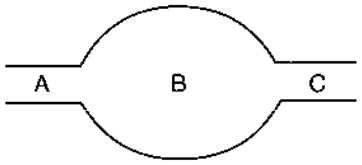


Figure V-1-13. Aortic Enlargement

Thus, because the aneurysm has a greater radius, its wall tension will be greater than that of the surrounding normal vessel segments.

Also, as the aneurysm enlarges, wall tension increases, and the vessel is more likely to burst.

This principle also is important in dilated heart failure, in which the increased chamber size places greater tension on the failing ventricle. This further reduces its performance.

Another type of aneurysm is referred to as a dissecting aneurysm. In systemic arterial disease, the high velocity in the aorta may damage the endothelial lining, allowing blood to flow between and dissect the layers of the aorta. This weakens the aortic wall and is considered a life-threatening condition.

Vessel Compliance

$$C = \frac{\Delta V}{\Delta P}$$

Compliance of a vessel can be calculated, but the resulting number is, for all practical purposes, meaningless. It is much more important to simply have a good concept of compliance and understand the differences in compliance among the vessels that make up the cardiovascular system.

Compliance is essentially how easily a vessel is stretched. If a vessel is easily stretched, it is considered very compliant. The opposite is noncompliant or stiff.

Elasticity is the inverse of compliance. A vessel that has high elasticity (a large tendency to rebound from a stretch) has low compliance.

CHARACTERISTICS OF SYSTEMIC VEINS

Systemic veins are about 20 times more compliant than systemic arteries.

Veins also contain about 70% of the systemic blood volume and thus represent the major blood reservoir.

In the venous system, then, a small change in pressure causes a large change in venous volume. For example, in a hemorrhage, venous pressure decreases. Because veins are very compliant vessels, this loss of distending pressure causes a significant passive constriction of the veins and a decrease in blood stored in those veins.

- The blood removed from the veins will now contribute to the circulating blood volume (cardiac output), a compensation for the consequences of hemorrhage.
- The sympathetic nerves innervating the veins will cause an active constriction and a further reduction in stored blood volume.

Volume loading (infusion of fluid) increases venous pressure. The increased pressure distends the veins; this is a passive dilation. The volume of fluid stored in the veins increases, which means that some of the infused volume will not contribute to cardiac output. The large volume and compliant nature of the veins act to buffer changes in venous return and cardiac output.

Because of the high compliance of veins, large increases of pressure occur mainly with substantial increases of volume, as in congestive heart failure, or with massive sympathetic activity that reduces compliance. Similarly, substantial decreases of central venous pressure occur with large loss of volume. An exception is the effect of posture, which can affect central venous pressure, even though blood volume has not changed.

The actual venous return to the heart is determined by the venous pressure gradient. This effect is summarized in Figure V-1-14.

ABBREVIATIONS

CVP = Central venous pressure

IPP = Intrapleural pressure

LH = Left heart

MABP = Mean arterial blood pressure

PVP = Peripheral venous pressure

RH = Right heart

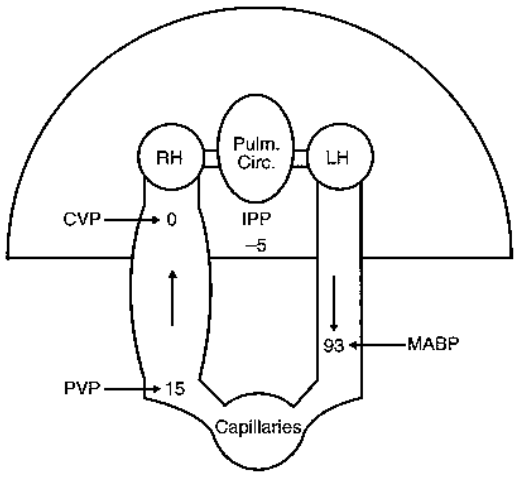


Figure V-1-14. Pressure Gradients in the Circulatory System

- Arteries are high pressure vessels but are very stiff and do not represent a significant blood reservoir.
- Veins are low pressure vessels but because they are very compliant, they are easily stretched and represent a large blood reservoir.

CHARACTERISTICS OF SYSTEMIC ARTERIES

Figure V-1-15 shows a pressure pulse for a major systemic artery.

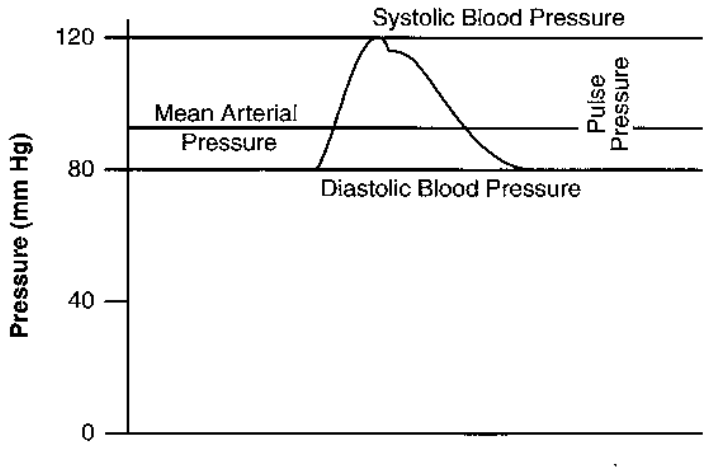


Figure V-1-15. Pulse Pressure and Mean Pressure

Pulse pressure = systolic–diastolic, or in the figure above: Pulse pressure = 120 – 80 = 40 mm Hg

Factors Affecting Systolic Pressure

- Systolic blood pressure is the highest pressure in the systemic arteries during the cardiac cycle.
- The main factor determining systolic blood pressure is stroke volume.
- An increase in stroke volume increases systolic blood pressure and a decrease in stroke volume decreases systolic blood pressure. For example, a decrease in heart rate or an increase in preload would increase systolic blood pressure.
- A decrease in the compliance of the systemic arteries will also increase systolic blood pressure.

Factors Affecting Diastolic Pressure

- Diastolic blood pressure is the lowest pressure in the systemic arteries during the cardiac cycle.
- The main factor determining diastolic blood pressure is total peripheral resistance, which is determined by the resistance of the arterioles.
- Dilation of the arterioles decreases diastolic blood pressure, and constriction of the arterioles increases diastolic blood pressure.
- A decrease in heart rate or stroke volume will also decrease diastolic blood pressure.

Factors Affecting Pulse Pressure

The following will increase (widen) pulse pressure:

- An increase in stroke volume (systolic increases more than diastolic)
- A decrease in vessel compliance (systolic increases and diastolic decreases)

The aorta is the most compliant artery in the systemic system. Peripheral arteries are more muscular and less compliant. Based on the preceding information, in Figure V-1-16 the pressure record on the left best represents the aorta, whereas the one on the right best represents the femoral artery.

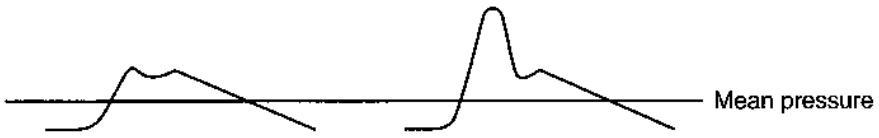


Figure V-1-16. Compliance and Pulse Pressure

The figure demonstrates that a compliant artery has a small pulse pressure and that a stiff artery has a large pulse pressure. Also, pulse pressure increases with age because compliance is decreasing. This can produce isolated systolic hypertension, in which mean pressure is normal because the elevated systolic pressure is associated with a reduced diastolic pressure.

Factors Affecting Mean Pressure

Mean pressure is pressure averaged over time. It is closer to diastolic pressure than to systolic pressure. Therefore, diastolic pressure is a better index of mean pressure than is systolic.

Mean pressure can be approximated by the following formulas:

Mean pressure = diastolic + 1/3 pulse pressure

= 2/3 diastolic pressure + 1/3 systolic pressure

Any formula that calculates mean pressure must give a value between systolic and diastolic but closer to diastolic than systolic.

Factors that affect mean pressure (the application of the Poiseuille equation to the systemic circuit):

Q = cardiac output

P_1 = aortic pressure (mean arterial pressure)

P_2 = pressure at the entrance of the right atrium

R = resistance of all vessels in the systemic circuit. This is referred to as total peripheral resistance (TPR).

Because the major component of TPR is the arterioles, TPR can be considered an index of arteriolar resistance.

Because P_1 is a very large number (100 mm Hg) and P_2 is a very small number that doesn't change dramatically in most situations, we can simplify the equation if we approximate P_2 as zero. Then:

$$CO = \frac{MAP}{TPR}$$

MAP = mean arterial pressure
CO = cardiac output
TPR = total peripheral resistance

or

$$\mathbf{MAP = CO \times TPR}$$

This equation simply states that:

- Mean arterial pressure (MAP), which is maintained close to 100 mm Hg, is determined by only two variables: cardiac output and TPR.
- CO can be considered circulating volume. The blood stored in the systemic veins and the pulmonary circuit would not be included in this volume.
- TPR is the resistance of all vessels in the systemic circuit. By far the largest component is the resistance in the arterioles.
- However, if venous or right atrial pressure (RAP) is severely increased, it must be taken into account when estimating TPR. In this case, the formula is:

$$(MAP - RAP) = CO \times TPR$$

or rearranged to solve for resistance: $TPR = (MAP - RAP)/CO$

Hemorrhage

The problem is the loss of CO or circulating blood volume. The increase in TPR via the carotid sinus reflex minimizes the loss of blood pressure. Because the reflex increase in TPR almost completely compensates in early hemorrhage, blood pressure is not a good index of blood loss following a hemorrhage.

Exercise

Dynamic, aerobic exercise produces minimal changes in blood pressure (actually a slight increase). The decrease in TPR, mainly due to the dilation of arterioles in the exercising muscle, is accompanied by an equivalent increase in CO with little change in MAP. For example, a threefold increase in CO would be the response if TPR decreased to a third of the resting level. With high-intensity exercise—especially static, such as weight lifting—physical compression of blood vessels during skeletal muscle contraction raises TPR. During the contraction, mean arterial pressure can increase greatly.

In the pulmonary circulation, P2 cannot be disregarded because left atrial pressure is generally higher (5 mm Hg) than right atrial pressure, and pulmonary arterial pressure is much lower (15 mm Hg) than systemic arterial pressure. Left atrial pressure is approximated as pulmonary capillary wedge pressure.

Poiseuille's equation, as illustrated below, can be used to estimate pulmonary vascular resistance.

$$\text{Pulmonary resistance} = \frac{\text{Mean pulmonary arterial pressure} - \text{Pulmonary wedge pressure}}{\text{Cardiac output}}$$

The Swan-Ganz catheter would provide both pressures in the numerator.

This is calculated in potential heart transplant recipients. If pulmonary resistance is elevated, the right heart transplant would be exposed to an increase in afterload and may fail.

THE EFFECT OF GRAVITY

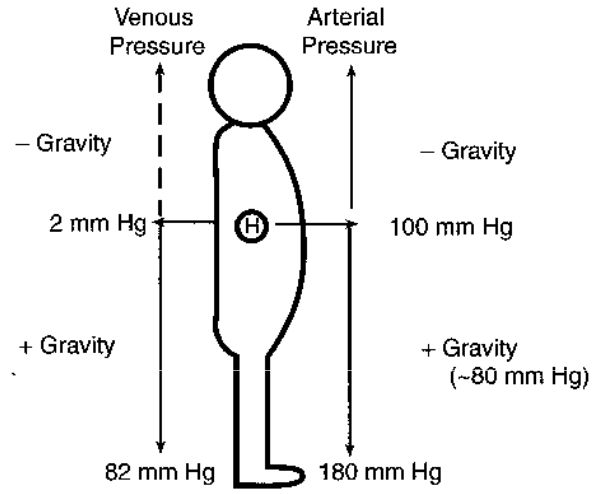


Figure V-1-17. Effect of Gravity

Upright Individual Summary

Below heart level, there are equal increases in systemic arterial and venous pressures (assuming no muscular action). Thus, the pressure difference between arteries and veins does not change.

Because veins are very compliant vessels, the higher pressures in the dependent veins mean a significant pooling of blood, a volume that is not contributing to cardiac output.

When a person goes from supine to an upright posture, the following important changes take place:

- Pressure in the dependent veins increases.
- Blood volume in the dependent veins increases.
- Circulating blood volume (CO) decreases.
- Blood pressure decreases.

Compensation via the carotid sinus reflex will include:

- TPR increases.
- Heart rate increases.

The changes induced by the carotid sinus return blood pressure toward the value in the supine position, but in most cases compensation will not be complete.

Above heart level, systemic arterial pressure progressively decreases.

Because venous pressure at heart level is close to zero, venous pressure quickly becomes subatmospheric (negative).

Surface veins above the heart cannot maintain a significant pressure below atmospheric; however, deep veins and those inside the cranium supported by the tissue can maintain a pressure that is significantly below atmospheric.

A consequence of the preceding is that a severed or punctured vein above heart level has the potential for introducing air into the system.

THE BARORECEPTOR REFLEX AND THE CONTROL OF BLOOD PRESSURE

Baroreceptor reflex: short-term regulation of blood pressure

Renin-angiotensin-aldosterone system: long-term regulation of blood pressure

Figure V-1-18 illustrates the main features of the baroreceptor reflex.

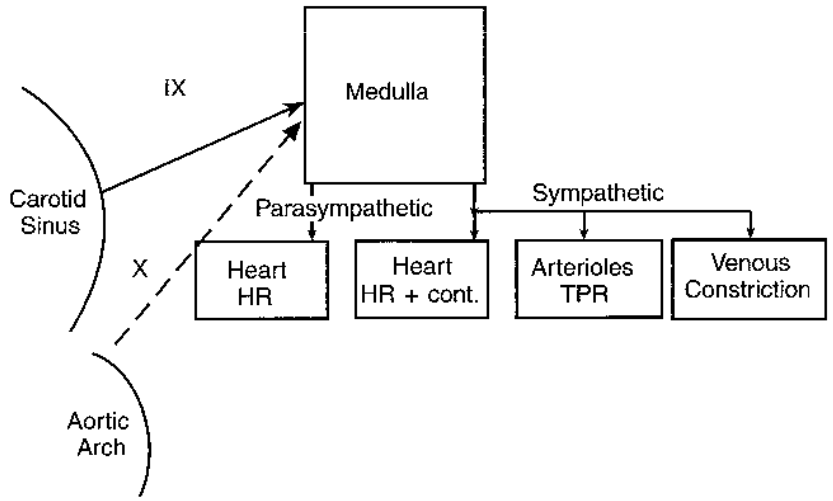


Figure V-1-18. Baroreflexes

$$MAP = CO \times TPR$$

A lowered blood pressure (MAP) leads to a rise in CO and TPR.

A rise in blood pressure leads to a decrease in CO and TPR.

The main receptors of the system are located in the carotid sinus. Here the receptors monitor the stretch of the vessel wall as an index of arterial blood pressure. The afferents are always active, with impulses traveling centrally. This is necessary if both increases and decreases in

blood pressure are to be detected. The medulla interprets only the afferent activity as an index of blood pressure. A rise in afferent activity signals an increase in blood pressure, and a loss of afferent activity signals a decrease in blood pressure.

The output is via the parasympathetic and sympathetic systems to change both CO and TPR in a direction to return blood pressure toward the indexed set point.

Table V-1-2. Reflex Changes for Specific Maneuvers

Condition	Afferent Activity	Parasympathetic Activity	Sympathetic Activity		
BP increase	↑	↑	↓		
BP decrease	↓	↓	↑	**BP**	**HR**
Carotid occlusion	↓	↓	↑	↑	↑
Carotid massage	↑	↑	↓	↓	↓
Cut afferents	↓	↓	↑	↑	↑
Lying to stand	↓	↓	↑	↑ toward normal	↑
Orthostatic hypotension					
Fluid loss					
Volume load	↑	↑	↓	↓ toward normal	↓
Weightlessness					

Chapter Summary

* The cardiovascular system consists of two circuits and two pumps connected in series.
* Systemic pressure decreases slightly through the arteries, decreases markedly through the arterioles, and then decreases only slightly more through the major veins. The loss of pressure is determined by regional resistance.
* The cross-sectional area increases from a minimum in the aorta to a maximum in the capillaries. Velocity of the blood is inversely related to a region's cross-sectional area.
* The main blood reservoir is the systemic veins.
* Of the factors affecting a vessel's resistance, radius is the most important. The radius of the arterioles determines total peripheral resistance.
* The cardiovascular system is a laminar flow system. The factors that promote turbulence include decreased fluid viscosity, large-diameter tubes, increased fluid velocity, and vessel branching.
* Structures connected in series produce high resistance, and flow is dependent and equal at all points.
* Mean arterial pressure is determined only by the circulating blood volume (cardiac output) and the resistance of the arterioles.
* Systemic organs are connected in parallel, which permits independent regulation of flow.
* Vessel wall tension is directly proportional to pressure and radius.
* The aorta is the most compliant artery, but veins are more compliant than arteries.
* Gravity causes the pooling of blood in the dependent veins. This blood does not contribute to cardiac output.
* The baroreceptor reflex alters parasympathetic and sympathetic outflow to minimize acute changes in blood pressure.

Regulation of Blood Flow and Pressure

MEASUREMENT OF CARDIAC OUTPUT USING THE FICK PRINCIPLE

The Fick principle can be utilized to calculate the blood flow through an organ.

Calculation of flow through the pulmonary circuit provides a measure of the CO.

$$\text{Flow} = \frac{\text{uptake}}{\text{A} - \text{V}}$$

Required data are: oxygen consumption of the organ

A – V oxygen content (concentration) difference across the organ (not PO_2)

Pulmonary venous (systemic arterial) oxygen content = 20 vol%
= 20 volumes O_2 per 100 volumes blood
= 20 mL O_2 per 100 mL blood
= 0.2 mL O_2 per mL blood

If pulmonary vessel data are not available, you may substitute arterial oxygen content for pulmonary venous blood and use venous oxygen content in place of pulmonary artery values.

Figure V-2-1 illustrates the situation in a normal resting individual.

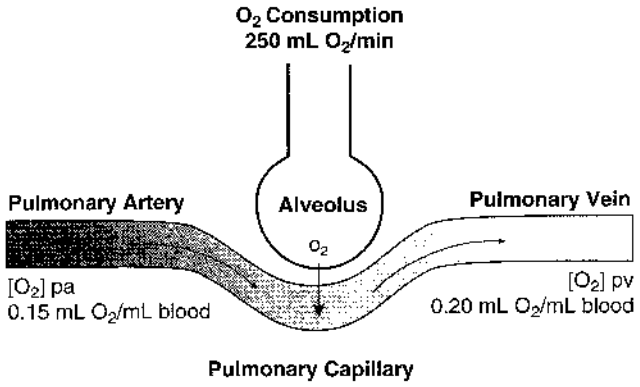


Figure V-2-1. Alveolar Oxygen Uptake

$$Q\,(\text{flow}) = \frac{\text{oxygen consumption}}{[O_2]\text{pv} - [O_2]\text{pa}}$$

$$= \frac{250\ \text{mL/min}}{0.20\ \text{mL/mL} - 0.15\ \text{mL/mL}} = 5{,}000\ \text{mL/min}$$

$$\text{Cardiac index} = \frac{\text{cardiac output}}{\text{body surface area}}$$

This would normalize the value for body size.

GENERAL CONCEPTS OF BLOOD FLOW REGULATION

Flow is regulated by constricting and dilating the smooth muscle surrounding the arterioles.

Intrinsic Regulation (Autoregulation)

The control mechanisms regulating the arteriolar smooth muscle are entirely within the organ itself.

- What is regulated is blood flow, not resistance. It is more correct to say that resistance is changed in order to regulate flow.
- No nerves or circulating substances are involved in autoregulation. Thus, the autonomic nervous system and circulating epinephrine have nothing to do with autoregulation.

There are two main theories that attempt to explain autoregulation. Of the two, the metabolic hypothesis has more support.

Metabolic hypothesis

- Tissue produces a vasodilatory metabolite that regulates flow, e.g., adenosine in the coronary circulation.
- A dilation of the arterioles is produced when the concentration of these metabolites increases in the tissue. The arterioles constrict if the tissue concentration decreases.

Myogenic hypothesis

- Increased perfusing pressure causes stretch of the arteriolar wall and the surrounding smooth muscle.
- Because an inherent property of the smooth muscle is to contract when stretched, the arteriole radius decreases, and flow does not increase significantly.
- This explanation cannot stand alone unless overcompensation to the stretch occurs; otherwise, positive feedback would cause the system to be unstable. Therefore, this mechanism is likely to be subordinate to the metabolic mechanism.

Major Characteristics of an Autoregulating Tissue

Blood flow should be independent of blood pressure.

This phenomenon is demonstrated for a theoretically perfect autoregulating tissue in Figure V-2-2. The range of pressure over which flow remains nearly constant is the **autoregulatory range.**

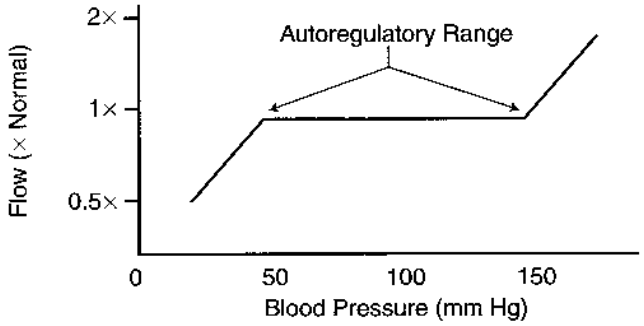


Figure V-2-2. Autoregulation

Blood flow in most cases is proportional to tissue metabolism.

Blood flow is independent of nervous reflexes (e.g., carotid sinus).

Autoregulating tissues include (tissues least affected by nervous reflexes):

- Cerebral circulation
- Coronary circulation
- Skeletal muscle vasculature during exercise

Control of renal blood flow is also commonly referred to as autoregulation even though it is partially controlled by neural and hormonal influences.

Extrinsic Regulation

These tissues are controlled by nervous and humoral factors originating outside the organ, e.g., resting skeletal muscle.

Figure V-2-3 illustrates an arteriole in skeletal muscle and the factors regulating flow under resting conditions.

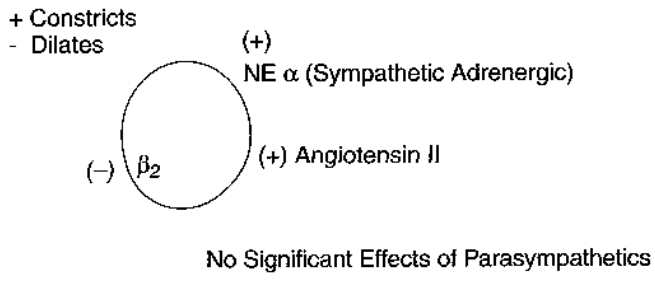


Figure V-2-3. Resting Skeletal Muscle Blood Flow

The main mechanism controlling flow in resting skeletal muscle and all other major extrinsically regulated systemic circuits is tonic changes in sympathetic adrenergic activity, i.e., norepinephrine acting on α receptors, causing constriction.

β receptors can contribute to the regulation; that is, circulating epinephrine acting on β_2 receptors can cause dilation. However, at high levels, circulating epinephrine has a vasoconstrictor effect through α-adrenergic receptors; so the response to epinephrine is dose-dependent.

Generally, the parasympathetic system does not affect arterioles, and thus it has little or no influence on TPR (exception: the penis).

Circulations with mainly extrinsic regulation (those most affected by nervous reflexes):

- Cutaneous circulation
- Resting skeletal muscle

Control of Resting versus Exercising Muscle

Resting muscle

Flow is controlled mainly by increasing or decreasing sympathetic α-adrenergic activity. But β_2 receptors can contribute to the regulation of blood flow.

Exercising muscle

The increase in flow is mainly via vasodilatory metabolites, but this cannot occur without a significant contribution via an increase in CO.

- β_2 activation via circulating epinephrine can contribute to the increase in flow.
- Sympathetic adrenergic nerves have no effect on flow in exercising muscle. (α receptors become less responsive to norepinephrine.)
- Thus, if there was an increase in sympathetic activity to an exercising muscle, flow would not be altered significantly by α receptor-mediated effects.

REGULATION OF BLOOD FLOW AT THE ORGAN LEVEL

Coronary Circulation

Coronary flow patterns

Characteristics of left coronary flow (flow to the left ventricular myocardium):

Left ventricular contraction causes severe mechanical compression of intramyocardial vessels. Therefore:

- Very little if any blood flow occurs during systole.
- Most of the blood flow is during diastole.

Characteristics of right coronary blood flow (flow to the right ventricular myocardium):

Right ventricular contraction causes modest mechanical compression of intramyocardial vessels. Therefore:

- Significant flow can occur during systole.
- The greatest flow under normal conditions is still during diastole.

Oxygenation

In the coronary circulation, the tissues extract almost all the oxygen they can from the blood, even under "basal" conditions. Therefore:

- The venous PO_2 is extremely low. It is the lowest venous PO_2 in a resting individual.
- Because the extraction of oxygen is almost maximal under resting conditions, increased oxygen delivery to the tissue can be accomplished only by an increased blood flow.
- In the coronary circulation, flow must match metabolism.
- Coronary blood flow is most closely related to cardiac tissue oxygen consumption.

Pumping action

Coronary blood flow (mL/min) is determined by the pumping action, or **stroke work** times heart rate, of the heart.

Increased pumping action means increased metabolism, which means increased production of vasodilatory metabolites, which means increased coronary flow.

Increased pump function occurs with:

- Exercise: increased volume work (more volume pumped at the same pressure)
- Increased arterial pressure (hypertension): increased pressure work (a similar volume pumped against a greater pressure)
- Pressure work has a higher oxygen cost than volume work; therefore, increased systolic ventricular pressure development will require a greater increase of coronary blood flow than a similar increase in stroke volume only.

Cerebral Circulation

Flow is proportional to arterial PCO_2.

Under normal conditions, arterial PCO_2 is the main factor regulating cerebral blood flow.

The final effector is smooth muscle hydrogen ions.

- Hypoventilation increases arterial PCO_2, thus it increases cerebral blood flow.
- Hyperventilation decreases arterial PCO_2, thus it decreases cerebral blood flow.

As long as arterial PO_2 is normal or above normal, cerebral blood flow will be regulated via arterial PCO_2. Therefore:

- If a normal person switches from breathing room air to 100% oxygen, there will be no significant change in cerebral blood flow.
- However, a (large) decrease in arterial PO_2 will increase cerebral blood flow. Under these conditions, it is the low arterial PO_2 that is determining flow.
- Baroreceptor reflexes do not affect flow.

Intracranial pressure is an important pathophysiologic factor that can affect cerebral blood flow.

Cutaneous Circulation

- Almost entirely controlled via sympathetic adrenergic nerves
- Large venous plexus innervated by sympathetics
- A-V shunts innervated by sympathetics
- Sympathetic stimulation to the skin will cause:
  - Constriction of arterioles and a decrease in blood flow
  - Constriction of the venous plexus and a decrease in blood volume in the skin

  - Increase in velocity of blood (decreased cross-sectional area)
- Sympathetic activity to the skin varies mainly with the body's need for heat exchange with the environment.

Increased skin temperature directly causes vasodilation, which increases heat loss.

Temperature regulation

Sensor represents the temperature-sensitive neurons in the anterior hypothalamus, whose firing rate reflects the temperature of the regional blood supply.

- Normal set point: oral 37°C (rectal + 0.5°C)
- Circadian rhythm: low point, morning; high point, evening

As illustrated in Figure V-2-4, the body does not lose the ability to regulate body temperature during a fever. It simply regulates body temperature at a higher set point.

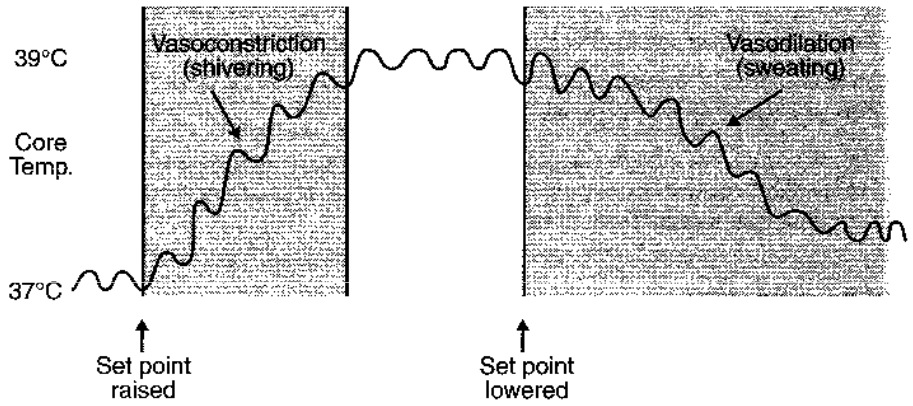


Figure V-2-4. Temperature Regulation

When a fever is developing, body temperature is rising toward the new higher set point. Under these conditions, heat-conserving and heat-generating mechanisms include:

- Shivering
- Cutaneous vasoconstriction

After a fever "breaks," the set point has returned to normal, and body temperature is decreasing. Heat-dissipating mechanisms include:

- Sweating (sympathetic cholinergics)
- Cutaneous vasodilation

Renal and Splanchnic Circulation

- A small change in blood pressure will invoke an autoregulatory response to maintain renal blood flow.
- Thus, under normal conditions, the renal and splanchnic circulations demonstrate autoregulation.

- Situations in which there is a large increase in sympathetic activity (e.g., hypotension) usually cause vasoconstriction and a decrease in blood flow.
- Renal circulation is greatly overperfused in terms of nutrient requirements, thus the venous PO_2 is high.

Pulmonary Circuit

Characteristics

- Low-pressure circuit, arterial = 15 mm Hg, venous = 5 mm Hg
- High flow, receives entire CO
- Low-resistance circuit
- Passive circuit; total flow not regulated
- Very compliant circuit; both arteries and veins are compliant vessels
- Hypoxic vasoconstriction (low alveolar PO_2 causes local vasoconstriction)
- Blood volume proportional to blood flow
  - Because of the passive nature of the pulmonary circuit, pulmonary pressures are proportional to the output of the right ventricle.
  - Because of the very compliant nature of the pulmonary circuit, large changes in the output of the right ventricle are associated with only small changes in pulmonary pressures.

Pulmonary response to exercise

- A large increase in cardiac output means increased volume pumped into the circuit. This will produce a rise in pulmonary pressures.
- Because of the passive, compliant nature of the circuit, the response to a rise in pressure is vessel dilation.
- This response leads to apical blood vessel recruitment. The overall response is a large decrease in resistance.
- Consequently, during exercise, there is only a slight increase in pulmonary pressures.
  - If the pulmonary circuit was not a passive, very compliant circuit, increasing the output of the right ventricle would cause pulmonary hypertension.

Pulmonary response to hemorrhage

- A large decrease in CO means decreased volume pumped into the circuit. This will produce a decrease in pulmonary pressures.
- Because of the passive, compliant nature of the circuit, the response to a decrease in pressure is vessel constriction. This results in a large increase in resistance.
- Consequently, during hemorrhage, there is often only a slight decrease in pulmonary pressures.
- Vessel constriction also means less blood is stored in this circuit.

Fetal Circulation

- The general features of the fetal circulatory system are shown in Figure V-2-5.
- The bolded numbers refer to the percent hemoglobin (%HbO_2) saturation.
- Of the fetal CO, 55% goes to the placenta.
- The umbilical vein and ductus venosus have highest %HbO_2 saturation (80%).
- When mixed with inferior vena caval blood (26% HbO_2), the %HbO_2 saturation of blood entering the right atrium is 67%.
- This blood is directed through the foramen ovale to the left atrium, left ventricle, and ascending aorta to perfuse the head and the forelimbs.
- Superior vena caval blood (40% HbO_2) is directed through the tricuspid valve into the right ventricle and pulmonary artery and shunted by the ductus arteriosus to the descending aorta. Shunting occurs because fetal pulmonary vascular resistance is very high, so 90% of the right ventricular output flows into the ductus arteriosus and only 10% to the lungs.
- The percent HbO_2 saturation of aortic blood is 60%.
- Fifty-five percent of the fetal CO goes through the placenta. At birth, the loss of the placental circulation increases systemic resistance. The subsequent rise in aortic blood pressure (as well as the fall in pulmonary arterial pressure caused by the expansion of the lungs) causes a reversal of flow in the ductus arteriosus, which leads to a large enough increase in left atrial pressure to close the foramen ovale.

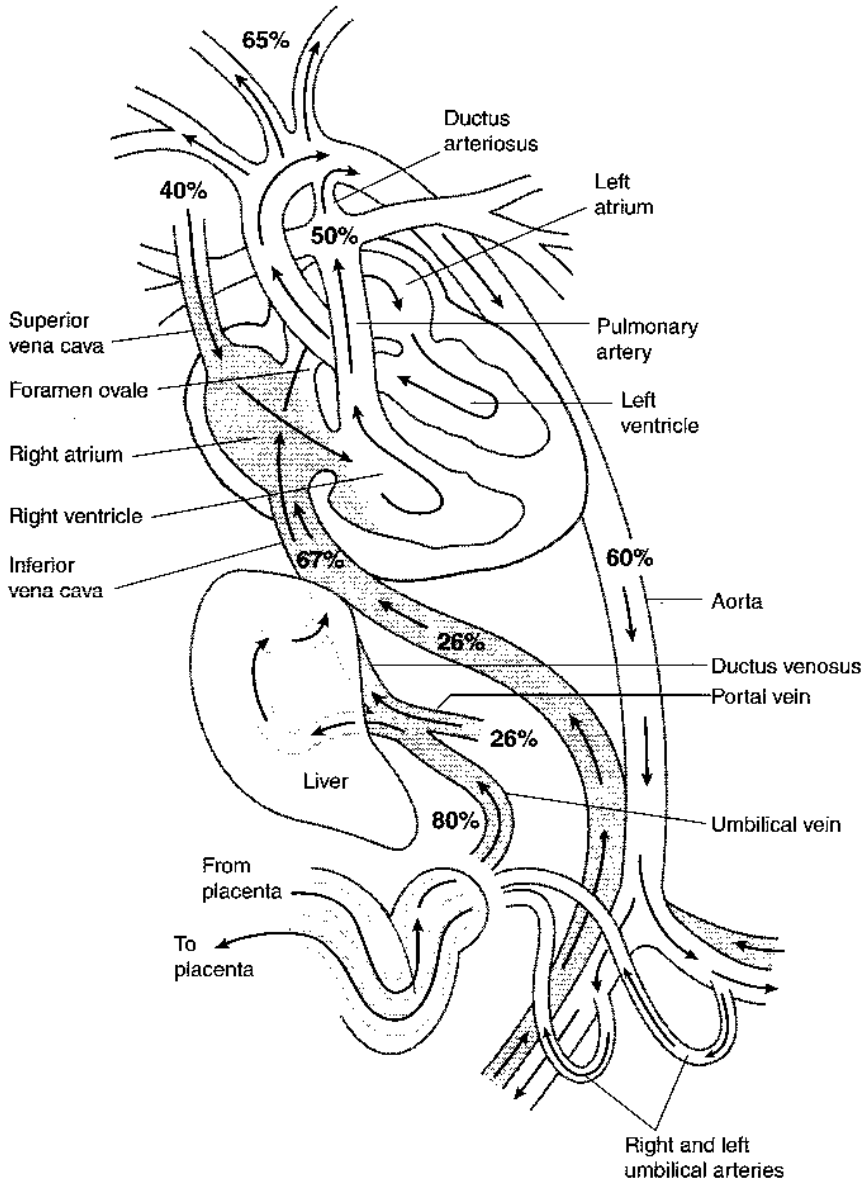


Figure V-2-5. Fetal Circulatory System

ARTERIAL-VENOUS DIFFERENCES (A SUPPLEMENTAL TOPIC)

General Principle

Figure V-2-6 illustrates the principle of calculating an arterial–venous (A-V) difference.

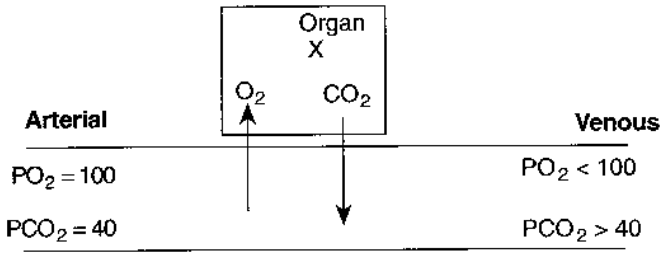


Figure V-2-6. Calculating an A-V Difference

Arterial-venous difference:

- is positive if substance extracted by the organ, e.g., O_2, substrates like glucose, lactate in heart muscle
- is negative if substance produced by the organ, e.g., CO_2, glucose in liver, lactate in skeletal muscle and ischemic heart muscle

Skeletal Muscle

- Resting muscle venous PO_2 ~ 45 mm Hg
- Exercising muscle venous PO_2 ~ 20 mm Hg

Review Questions

1. What is the A-V PO_2 difference in this resting muscle?
2. What is the A-V PO_2 difference in this exercising muscle?
3. What happens to the A-V difference with exercise?
   A. increase
   B. decrease
   C. no change
4. During exercise, increased oxygen delivery to the muscle is accomplished by:
   A. increased blood flow
   B. increased extraction
   C. both
5. With exercise, which increases more in skeletal muscle, flow or metabolism?
6. How does flow versus metabolism change in the heart with exercise?
7. How does the A-V PO_2 difference in the renal circuit compare with the coronary circuit?
8. Assuming no effect on metabolism, what consequences does a vasodilatory drug have on the A-V PO_2 difference in resting skeletal muscle?
9. What are the direct effects of an α agonist on the A-V PO_2 difference in resting skeletal muscle?

Answers

1. **(Same for question 2.)** The systemic arterial PO_2 is close to 100 mm Hg under resting conditions and does not change significantly during exercise.

   Thus, the resting A-V difference is:

   100 – 45 = 55 mm Hg

   During exercise, it will be:

   100 – 20 = 80 mm Hg

3. **Answer: A.** The greater extraction of oxygen during exercise increases the A-V difference.

4. **Answer: C.** During exercise, vasodilatory metabolites lower skeletal muscle vascular resistance, and flow increases. Increased flow means increased oxygen delivery. Even though flow increases, oxygen extraction increases. Therefore, C is the best answer.

5. If flow (oxygen delivery) kept pace with increased tissue demands during exercise, there would be no change in extraction; that is, if both flow and metabolism doubled, venous PO_2 would be unchanged. If metabolism increased more than flow, increased extraction would be necessary to meet tissue oxygen demands. Because extraction does increase in exercising muscle, there is a greater rise in metabolism than blood flow.

6. In the coronary circuit, oxygen extraction is close to the maximum under resting conditions. Therefore, increased extraction cannot be utilized effectively to meet any increased tissue oxygen demands. Flow must increase in proportion to metabolism in order to meet tissue demands. These two variables are directly proportional in the healthy heart.

7. In the coronary circuit, because oxygen extraction is maximal, there is a large A-V difference.

   i.e., PaO_2 = 100 mm Hg; coronary sinus PO_2 = 20 mm Hg
   A-V = 100 – 20 = 80 mm Hg

   The renal circuit is overperfused in terms of nutrient supply. Much more oxygen than is required flows through the renal circulation. Thus, less oxygen is extracted per mL of blood. Under these conditions, venous PO_2 will be higher than most systemic tissues. This will translate into a low A-V difference.

8. Vasodilation increases flow and oxygen delivery. If metabolism does not change, the amount of oxygen needed per unit of time remains unchanged. This oxygen will now be removed from a greater volume of blood. Thus, less oxygen is removed from each mL of blood, and the venous PO_2 will be higher. A higher venous PO_2 means a lower A-V difference.

9. The α agonist will constrict arterioles and reduce blood flow and oxygen delivery. The only way to maintain the same flow of oxygen to the tissue would be to increase extraction. This reduces venous PO_2 and increases the A-V difference.

BASIC ALTERATIONS DURING EXERCISE

The following assumes the person is in a steady state, performing moderate exercise at sea level.

Pulmonary Circuit

- Blood flow (CO): large increase
- Pulmonary arterial pressure: slight increase
- Pulmonary vascular resistance: large decrease
- Pulmonary blood volume: increase
- Number of perfused capillaries: increase
- Capillary surface area: increase, which means increased rate of gas exchange

Systemic Circuit

Arterial system

- PO_2: no significant change, hemoglobin still fully saturated
- PCO_2: no significant change, increase in ventilation proportional to increase in metabolism
- pH: no change or a decrease due mainly to the production of lactic acid
- Mean arterial pressure: slight increase
- Body temperature: slight increase

- Blood flow: large increase
- Vascular resistance (TPR): large decrease, dilation of skeletal muscle beds

Venous system

- PO_2: decrease
- PCO_2: increase

Regional Circulations

Exercising skeletal muscle

- Blood flow increases.
- Vascular resistance decreases.
- Capillary pressure increases.
- Capillary filtration increases.
- Lymph flow increases.
- Venous PO_2 decreases and can reach extremely low levels.
- Extraction of oxygen increases.

Cutaneous blood flow

Initial decrease, then an increase to dissipate heat

Coronary blood flow

Increase due to increase in volume work of the heart

Cerebral blood flow

No significant change (arterial CO_2 remains unchanged)

Renal and GI blood flow

Any change would be a decrease. This is more likely in the splanchnic circuit

Heart

Exercise produces an increase in the volume work of the heart that is mainly carried out by an increase in heart rate rather than an increase in stroke volume.

In light and moderate exercise, there may be no increase in preload. Preload does increase in heavy exercise.

Physical conditioning

- Regular exercise will raise maximal oxygen consumption ($\dot{V}O_2max$) by:

  Increasing the ability to deliver oxygen to the active muscles. It does this by increasing the CO.

  The resting conditioned heart has a lower heart rate but a greater stroke volume (SV) than does the resting unconditioned heart.

  During exercise, there is an increase in stroke volume, as much as 35% above resting levels.

  However, the maximal heart rate remains similar to that of untrained individuals.

- Regular exercise also increases the ability of muscles to utilize oxygen. There are:

  An increased number of arterioles, which decrease minimal resistance during exercise.

  An increased capillary density, which increases the surface area and decreases diffusion distance.

  An increased number of oxidative enzymes in the mitochondria.

Chapter Summary

* The production of vasodilatory metabolites best explains the control of blood flow in autoregulating systemic tissues.
* Sympathetic adrenergic nerves represent the main control in extrinsically regulated systemic tissues.
* Resting skeletal muscle exhibits extrinsic regulation, but exercising muscle autoregulates.
* Mechanical compression of the intramyocardial vessels restricts perfusion to the myocardium during systole.
* Because oxygen extraction is almost complete from the blood perfusing the myocardium, coronary flow must match myocardial metabolism.
* The main factor regulating cerebral blood flow is arterial carbon dioxide.
* The cutaneous circulation exhibits extrinsic regulation, and flow responds to the need for heat exchange with the environment.
* Normally, the kidney exhibits strong autoregulation but constricts, resulting in a loss in renal function, with a large decrease in blood pressure.
* The passive, compliant nature of the pulmonary circuit minimizes changes in pulmonary pressures with large changes in cardiac output.

SECTION VI

Cardiac Cycle and Valvular Heart Disease

Cardiac Cycle and Valvular Heart Disease

NORMAL CARDIAC CYCLE

Figure VI-1-1 illustrates the most important features of the cardiac cycle.

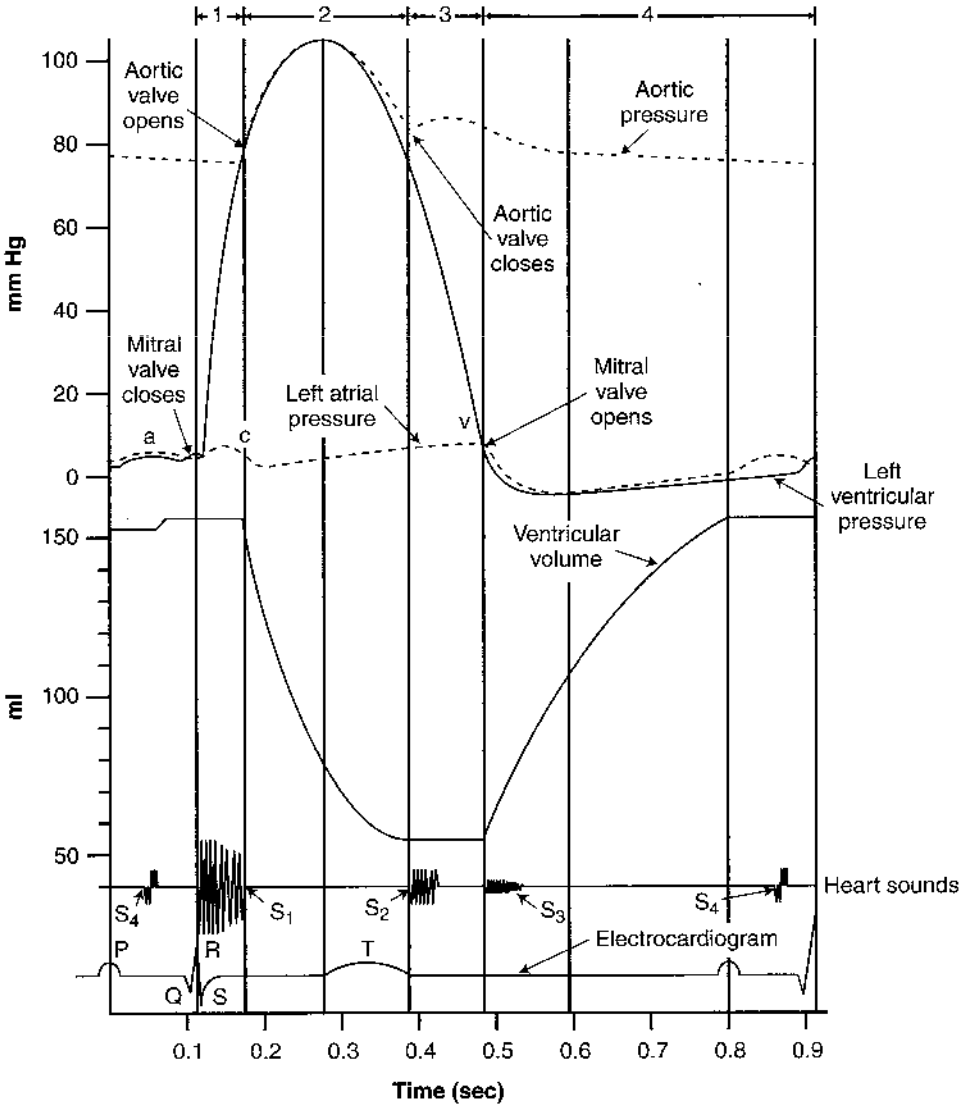


Figure VI-1-1. Cardiac Cycle

The most important aspects of Figure VI-1-1 are the following:

- → QRS → contraction of ventricle → rise in ventricular pressure above atrial pressure → final closure of mitral valve
- It is always a pressure difference that causes the valves to open or close.
- Closure of the mitral valve terminates the ventricular filling phase and begins isovolumetric contraction.
- Isovolumetric contraction—no change in ventricular volume, and both valves (mitral, aortic) closed. Ventricular pressure is increasing, and volume is equivalent to end-diastolic volume.
- Opening of the aortic valve terminates isovolumetric contraction and begins the ejection phase. Aortic valve opens because pressure in the ventricle slightly exceeds aortic pressure.
- Ejection Phase—ventricular volume decreases, but most rapidly in early stages. Ventricular and aortic pressures increase initially but decrease later in phase.
- Closure of the aortic valve terminates the ejection phase and begins isovolumetric relaxation. The aortic valve closes because pressure in the ventricle goes below aortic pressure. Closure of the aortic valve creates the dicrotic notch.
- Isovolumetric relaxation—no change in ventricular volume, and both valves (mitral, aortic) closed. Ventricular pressure is decreasing, and volume is equivalent to end-systolic volume.
- Opening of the mitral valve terminates isovolumetric relaxation and begins the filling phase. Mitral valve opens because pressure in the ventricle goes below atrial pressure.
- Filling Phase—the final relaxation of the ventricle occurs after the mitral valve opens and produces a rapid early filling of the ventricle. This rapid inflow will in some cases induce the third heart sound. Final increase in ventricular volume is due to atrial contraction, which is responsible for the fourth heart sound. Atrial contraction normally is not important in the filling of the ventricle unless heart rate is elevated as occurs during exercise or in the case of a stiff ventricular chamber.

Heart Sounds

The systolic sounds are due to the sudden closure of the heart valves. Normally the valves on the left side of the heart close first. Valves on the right side open first.

Systolic sounds

S1: Produced by the closure of the mitral and tricuspid valves. The valves close with only a separation of about 0.01 seconds which the human ear can appreciate only as a single sound. One exception is in the right bundle branch block where an audible split can be detected due to a delay in the closure of the tricuspid valve.

S2: Produced by the closure of the aortic (A2 component) and pulmonic valves (P2 component). They are heard as a single sound during expiration but during inspiration the increased output of the right heart will cause a physiological splitting. The following figure illustrates several situations where splitting of the second heart sound may become audible.

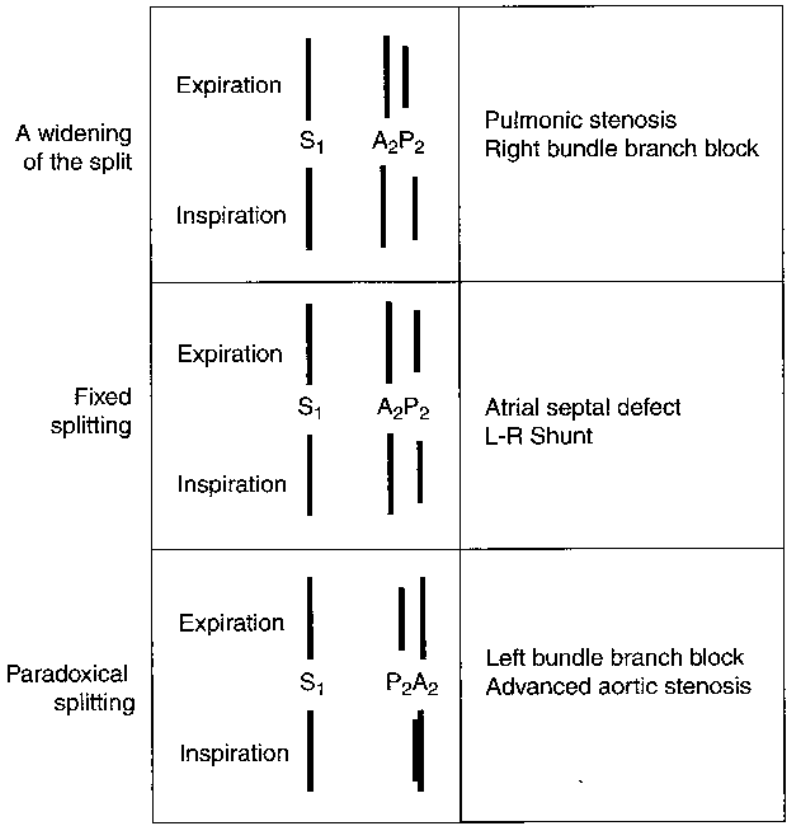


Figure VI-1-2. Abnormal Splitting of the Second Heart Sound (S_2)

S3: When it is present, occurs just after the opening of the AV valves during the rapid filling of the ventricle. It tends to be produced by the rapid expansion of a very compliant ventricle and is a normal finding in children and young adults. In older adults it occurs with volume overload and often is a sign of cardiac disease.

S4: Coincident with atrial contraction and is produced when the atrium contracts against a stiff ventricle. Examples include concentric hypertrophy and myocardial infarction.

Venous Pulse

Figure VI-1-3 provides an example of a normal jugular venous pulse tracing. The jugular pulse is generated by changes on the right side of the heart. The pressures will generally vary with the respiratory cycle and are generally read at the end of expiration when intrapleural pressure is at its closest point to zero.

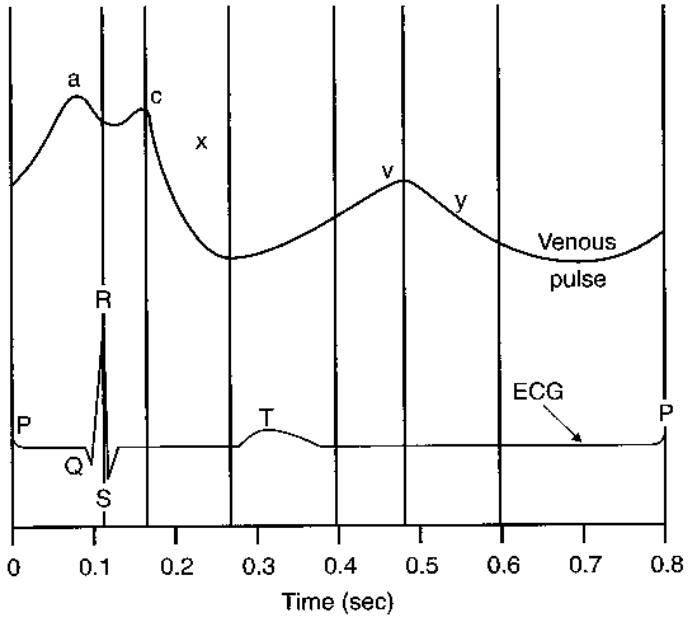


Figure VI-1-3. Venous Pulse and the ECG

a wave

- Highest deflection of the venous pulse and produced by the contraction of the right atrium
- Correlates with the PR interval (see figure)
- Is prominent in a stiff ventricle, pulmonic stenosis and insufficiency
- Is absent in atrial fibrillation and other atrial arrhythmias

c wave

- Mainly due to the bulging of the tricuspid valve into the atrium (rise in right atrial pressure)
- Occurs near the beginning of ventricular contraction
- Is often not seen during the recording of the venous pulse

x descent

- Produced by a decreasing atrial pressure during atrial relaxation
- Separated into two segments when the c wave is recorded
- Alteration would occur with atrial fibrillation and tricuspid insufficiency

v wave

- Produced by the filling of the atrium during ventricular systole when the tricuspid valve is closed
- Peak corresponds to T wave of the EKG and the opening of the tricuspid valve
- A prominent v wave would occur in tricuspid insufficiency and right heart failure

y descent

- Produced by the rapid filling of the right ventricle immediately after the opening of the tricuspid valve
- A more prominent wave in tricuspid insufficiency and a blunted wave in tricuspid stenosis.

Some abnormal venous pulses are shown in the following figure.

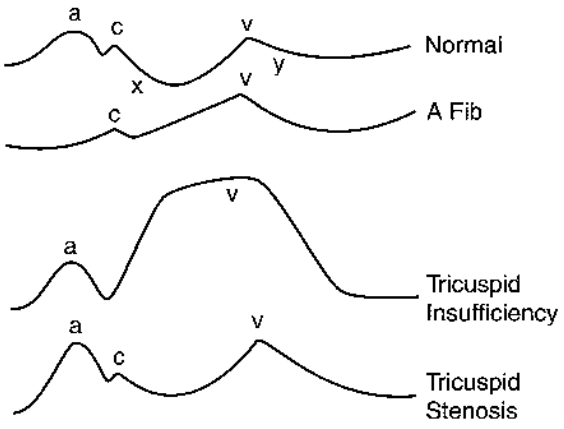


Figure VI-1-4. Normal Versus Abnormal Jugular Pulses

Similar recordings to the systemic venous pulse are obtained when recording pulmonary capillary wedge pressure. Left atrium mechanical events are transmitted in a retrograde manner, although they are somewhat damped and delayed. The figure below shows the pressure recording from the tip of a Swan-Ganz catheter inserted through a systemic vein through the right side of the heart into the pulmonary circulation and finally with the tip wedged in a small pulmonary artery. The pressure recorded at the tip of the catheter is referred to as pulmonary capillary wedge pressure and is close to left atrial pressure and is an index of preload on the left ventricle.

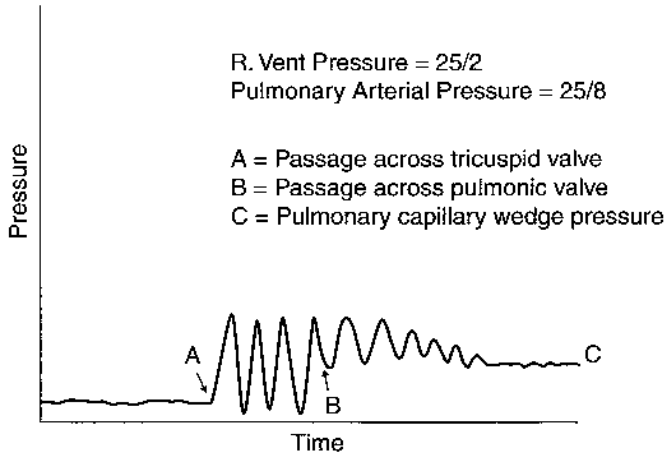


Figure VI-1-5. Passage of a Swan-Ganz Catheter From a Systemic Vein Through the Right Heat, Down the Pulmonary Arterial System Until it Becomes Wedged in a Small Artery

PRESSURE-VOLUME LOOPS

Figure VI-1-6 shows the major features of a left ventricular pressure–volume loop.

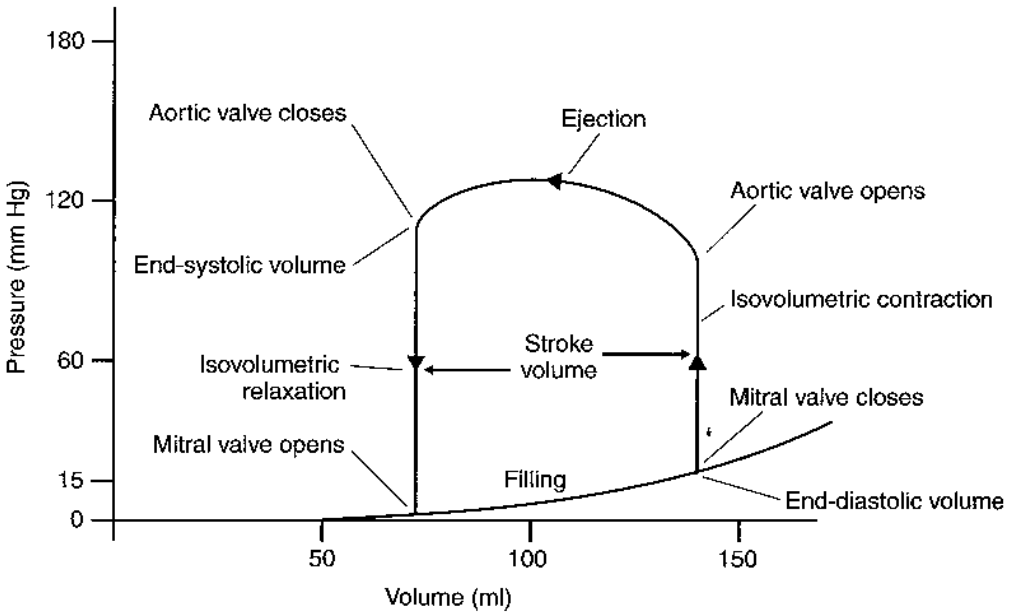


Figure VI-1-6. Left Ventricular Pressure–Volume Loop

- Most of the energy consumption occurs during isovolumetric contraction.
- Most of the work is performed during the ejection phase.

Mechanically Altered States

Aortic insufficiency: Increased preload, increased stroke volume, increased ventricular systolic pressure

Heart failure (decreased contractility): Decreased ventricular systolic pressure, increased preload, loop shifts to the right

Essential hypertension (aortic stenosis): Increased ventricular systolic pressure, little change in preload in the early stages

Increased contractility: Increased ventricular systolic pressure, decreased preload, increased ejection fraction, loop shifts to the left

Exercise: Increased ventricular systolic pressure, increased ejection fraction, no significant change in preload except in heavy exercise, when it can increase

VALVULAR PROBLEMS

Stenosis of valves usually consists of chronic problems which develop slowly over time. Valvular insufficiency problems can be acute or chronic, the consequences of which can be quite different.

Aortic Stenosis

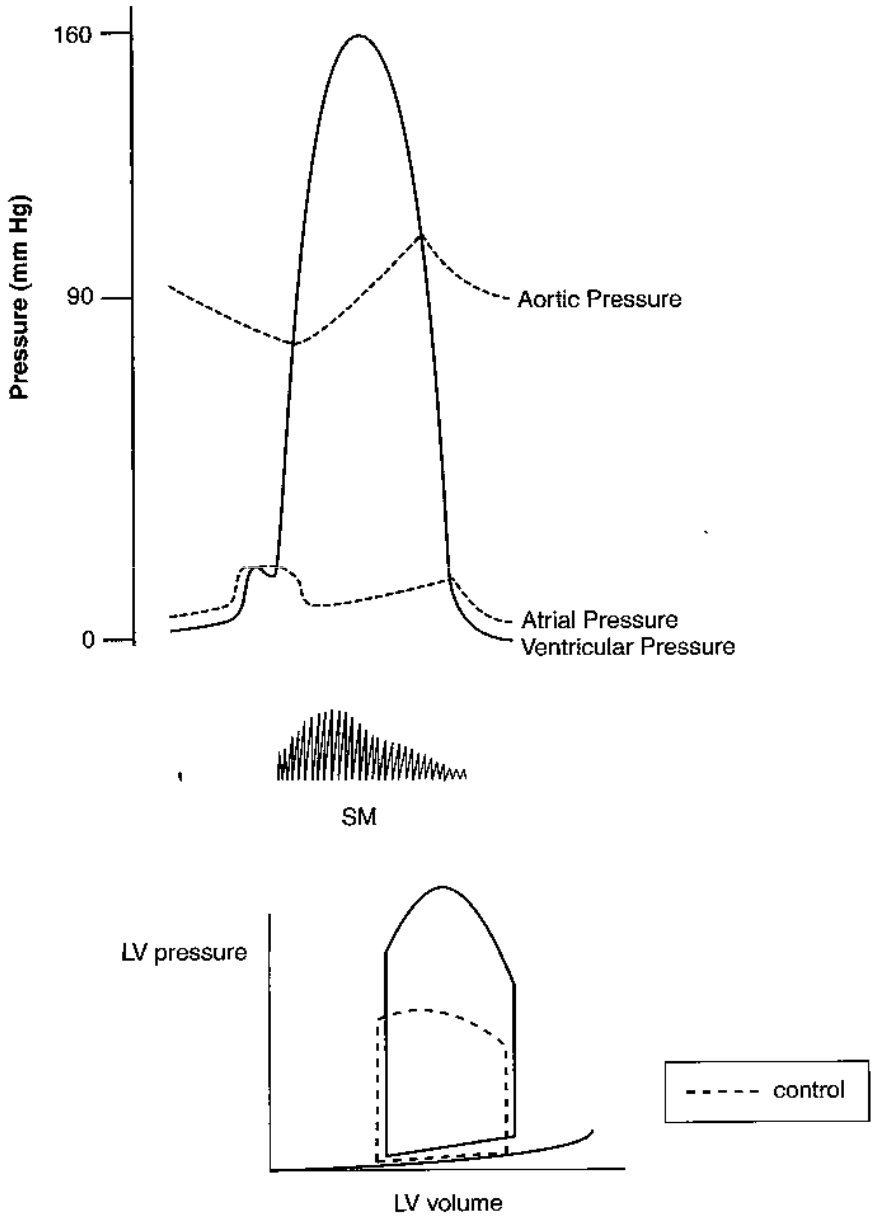


Figure VI-1-7. Aortic Stenosis

- Pathologic thickening and fusion of the valve leaflets that decreases the open valve area, creating a major resistance point in series with the systemic circuit.
- Large loss in pressure moving the blood through the narrow opening.
- Ventricular systolic pressure increases (increased afterload) to overcome the increased resistance of the aortic valve.
- Pressure overload of the left ventricle leads to a compensatory concentric hypertrophy which leads to decreased ventricular compliance (diastolic dysfunction) and coronary perfusion problems and eventually systolic dysfunction.
- Prominent a wave of the left atrium as the left ventricle becomes more dependent on atrial contraction for filling.
- Mean aortic pressure is maintained in the normal range in the early stages of the disorder.
- There is a pressure gradient between the left ventricle and aorta during ejection.
- Systolic murmur that begins after S1 (midsystolic) which is crescendo-decrescendo in intensity.
- Slow closure of the aortic valve can cause a paradoxical splitting of the second heart sound (aortic valve closes after the pulmonic)

Aortic Insufficiency

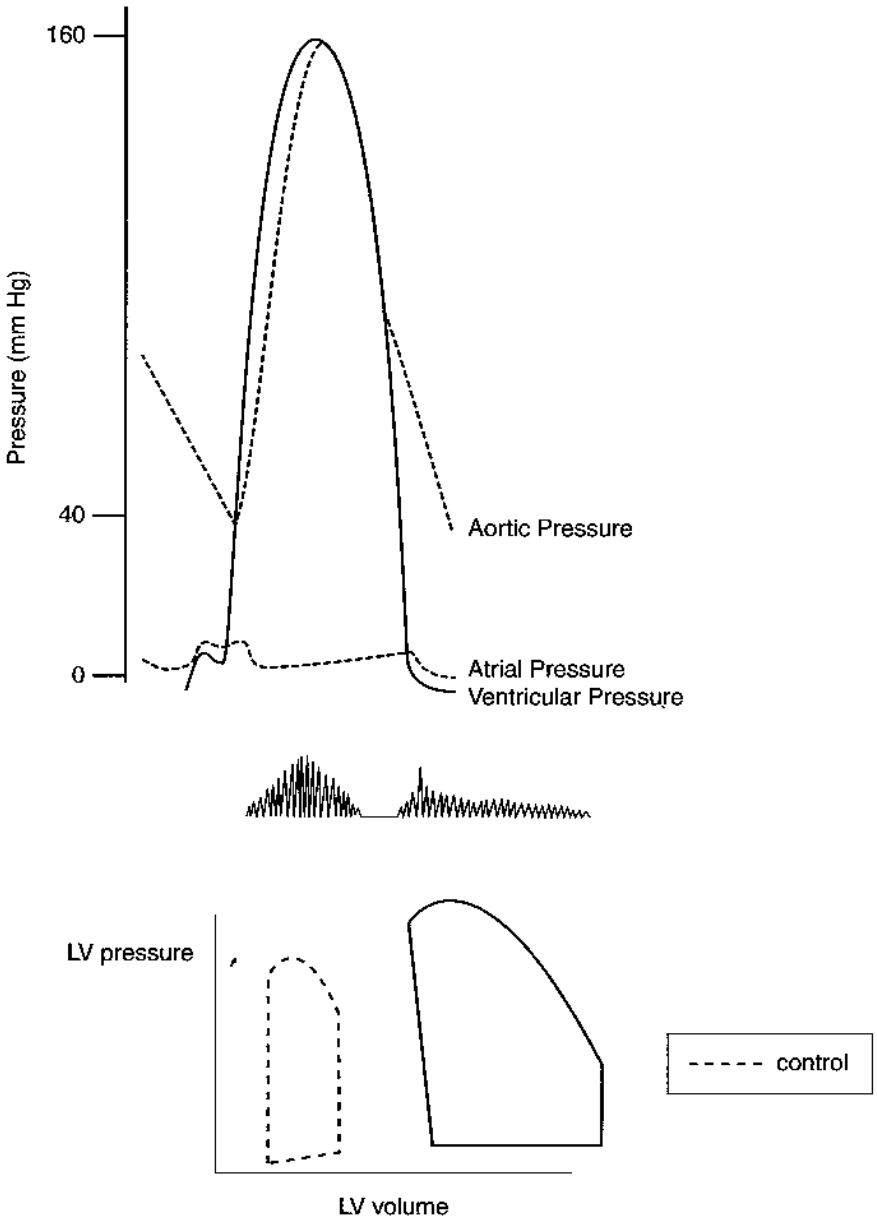


Figure VI-1-8. Aortic Insufficiency (Regurgitation)

The aortic valve does not close properly at the beginning of diastole. As a result, during diastole there is retrograde flow from the aorta into the ventricle. The amount of blood regurgitated into the left ventricle during diastole may be as much as 60–70% of the amount ejected during systole.

- Acute insufficiency does not allow development of compensatory mechanisms, which can lead to pulmonary edema and circulatory collapse.
- Very large left ventricles are seen in aortic insufficiency. Large increase in LVEDV (increase preload) but close to normal end diastolic pressures.
- Ventricular failure raises pulmonary pressures and causes dyspnea.
- Increased preload causes increased stroke volume, which results in increased ventricular and aortic systolic pressures.
- Retrograde flow from the aorta to the left ventricle produces a low aortic diastolic pressure.
- There is no true isovolumetric relaxation and a reduced period of isovolumetric contraction.
- Aortic insufficiency is characterized by a large aortic pulse pressure and a low aortic diastolic pressure.
- Dilation of the ventricle produces a compensatory eccentric hypertrophy.
- Diastolic murmur begins at S2 but may also be accompanied by a systolic murmur

itral Stenosis

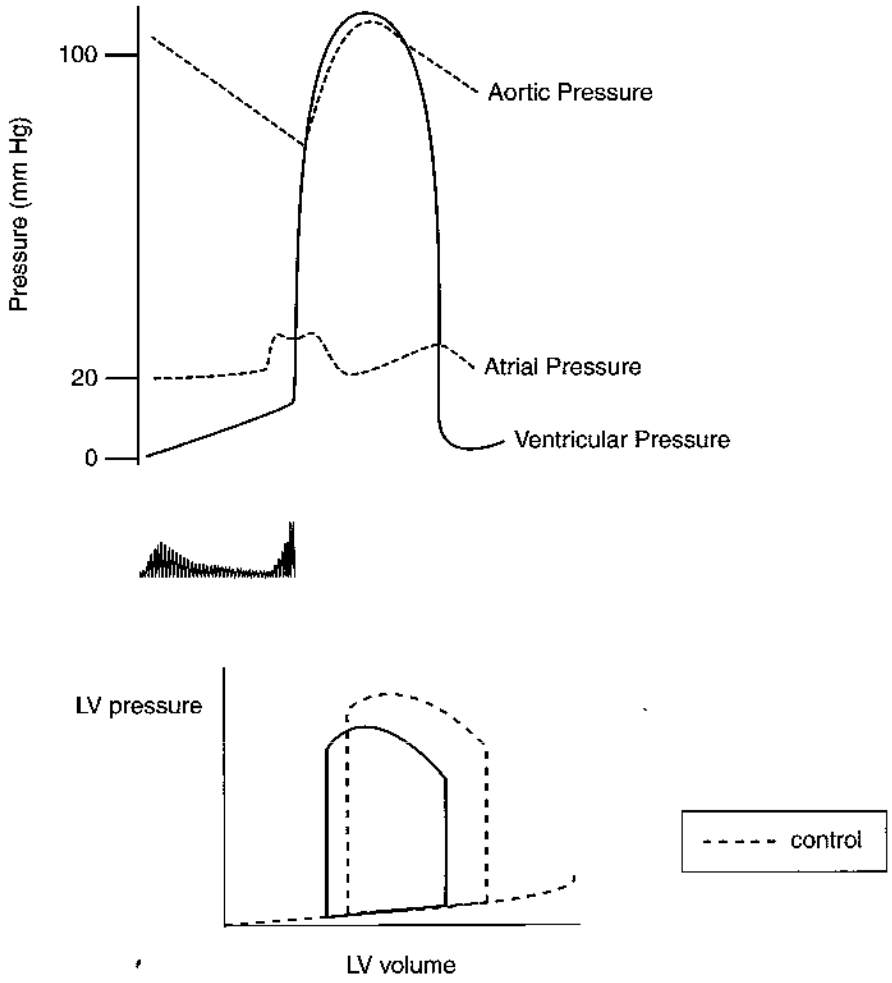


Figure VI-1-9. Mitral Stenosis

- A narrow mitral valve impairs emptying of the left atrium (LA) into the left ventricle (LV) during diastole. This creates a pressure gradient between the atrium and ventricle during filling.
- Pressure and volume can be dramatically elevated in the left atrium, dilation of the left atrium over time, which is accelerated with atrial fibrillation.
- Thrombi appear in the enlarged left atrium
- Increased left atrial pressures transmitted to the pulmonary circulation and the right heart.
- Little change or a decrease in the size of the left ventricle. Systolic function normal.
- Diastolic murmur begins after S2.

Mitral Insufficiency

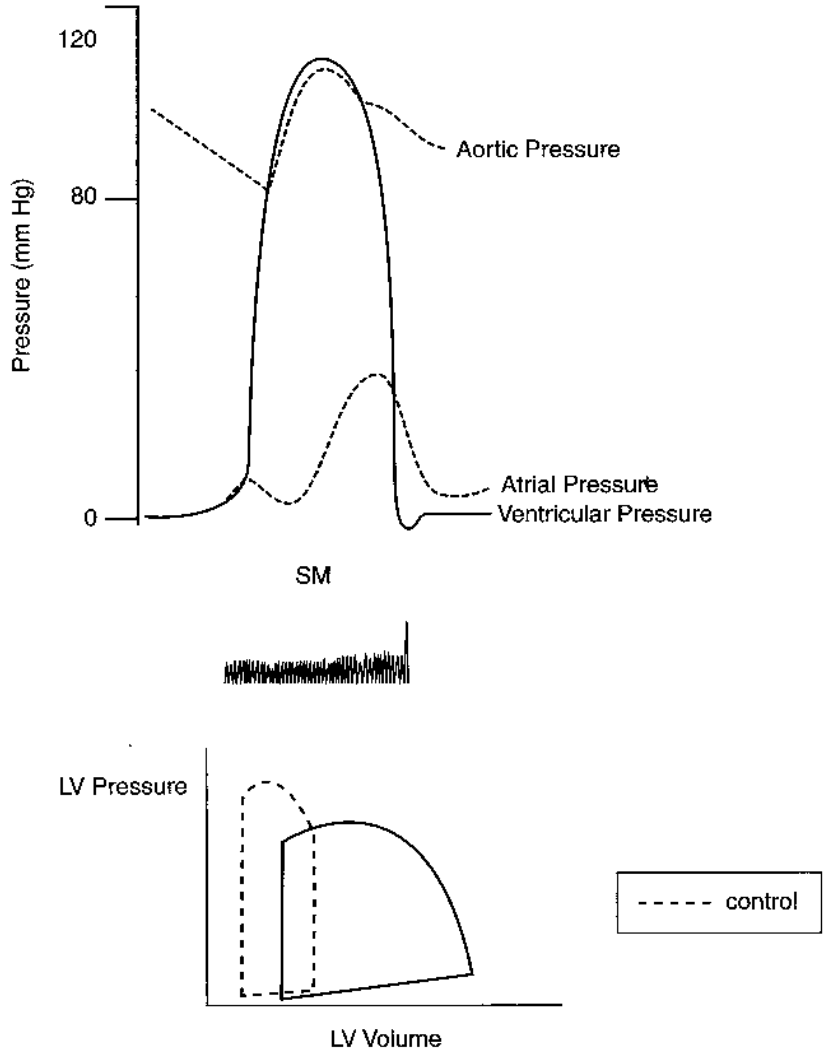


Figure VI-1-10. Mitral Insufficiency (Regurgitation)

- Acute mitral insufficiency can cause a sudden dramatic rise in pulmonary pressures and pulmonary edema.
- Can result from structural abnormalities in the valve itself, papillary muscles, chordae tendinae, or possibly a structural change in the mitral annulus.
- No true isovolumetric contraction. Regurgitation of blood from the left ventricle to the left atrium throughout ventricular systole.
- Atrial volumes and pressures increased but chronic dilation of the atrium prevents a dramatic rise in atrial pressures.
- Ventricular volumes and pressures are increased during diastole, but there is no pressure gradient between the atrium and ventricle.
- Increased preload but with normal or reduced afterload.
- Systolic murmur that begins at S1 (pansystolic).

MURMURS

Sounds Created by Turbulent Flow

Causes include:

- Stenosis, e.g., aortic stenosis
- High output, low viscosity, e.g., anemia
- Dilated chamber, e.g., aortic aneurysm
- Reverse flow across a heart valve, e.g., valvular insufficiency
- Shunting of blood, e.g., ventricular septal defect, patent ductus

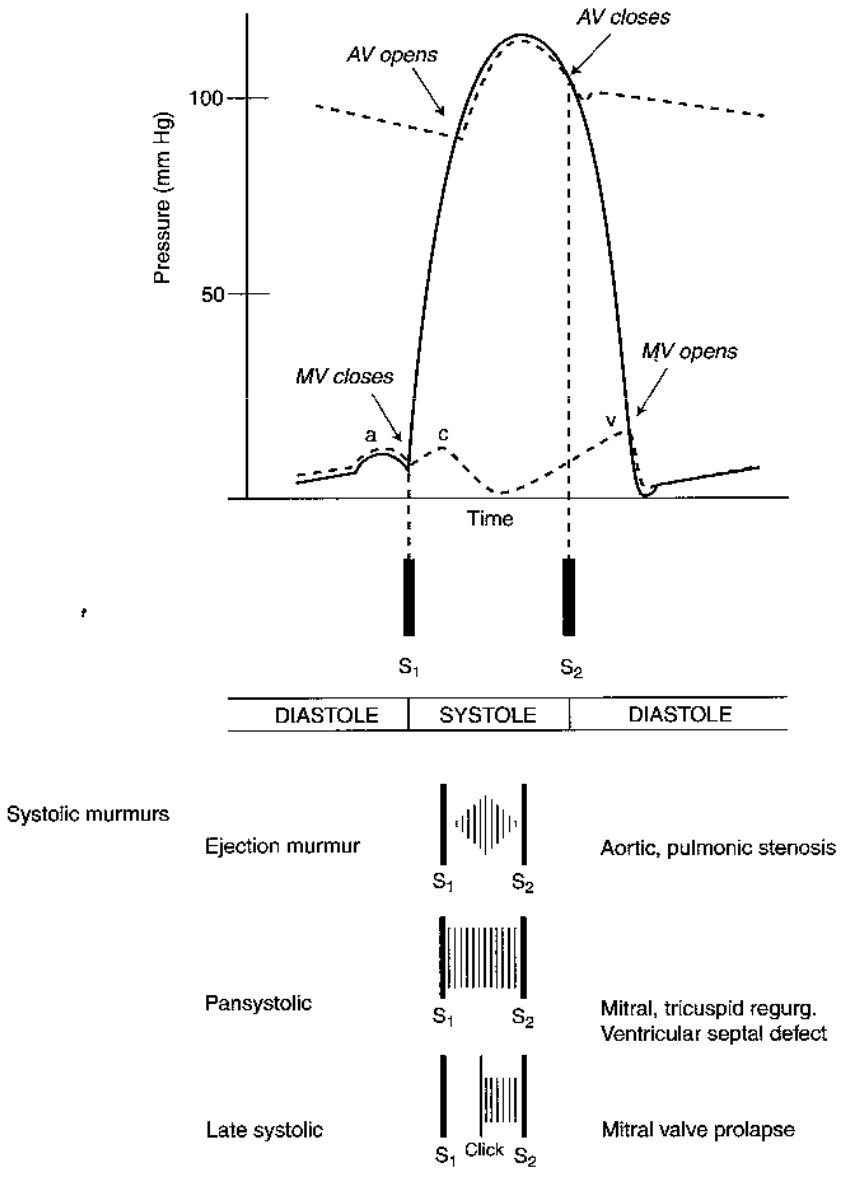
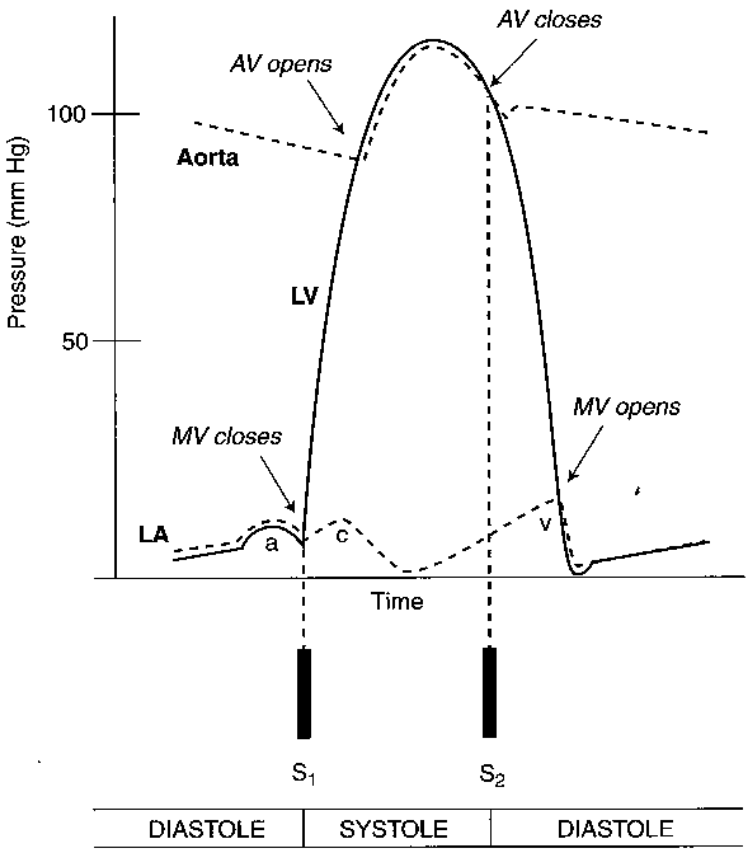
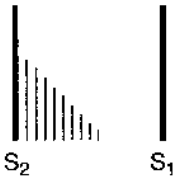


Figure VI-1-11



Diastolic murmurs

Early: aortic and pulmonic regurg.



Mid-to-late: mitral and tricuspid stenosis

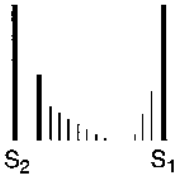


Figure VI-1-12

Chapter Summary

* The cardiac cycle consists of isovolumetric contraction followed by the ejection phase followed by isovolumetric relaxation followed by the filling phase.
* The heart valves normally close on the left side before they close on the right side.
* S1 the first systolic sound is due to the closure of the AV valves, and S2 the second systolic sound is due to the closure of the aortic and pulmonic valves.
* The diastolic sounds S3 and S4 are often not heard.
* An increased output of the right heart as occurs during inspiration produces an audible splitting of the second heart sound.
* The venous pulse recorded from a systemic vein reflects right heart events.
* A pressure–volume loop represents the work performed by the ventricle during a single cardiac cycle.
* Aortic stenosis increases afterload and produces a pressure gradient between the ventricle and aorta during ejection (midsystolic murmur).
* Aortic insufficiency increases preload and produces a retrograde flow from the aorta into the ventricle during isovolumetric relaxation (diastolic murmur begins at S2).
* Mitral stenosis increases left atrial volume and pressure, but ventricular volumes and pressures are normal or reduced (diastolic murmur begins after S2).
* Mitral insufficiency increases volumes and pressures in the atrium and ventricle (systolic murmur begins at S2).

SECTION VII

Respiration

Lung Mechanics

UNG VOLUMES AND THEIR MEASUREMENT

gure VII-1-1 shows graphically the relationships among the various lung volumes and capacities. linical measurements of specific volumes and capacities provide insights into lung function and ıe origin of disease processes. Those that provide the greatest information display an *.

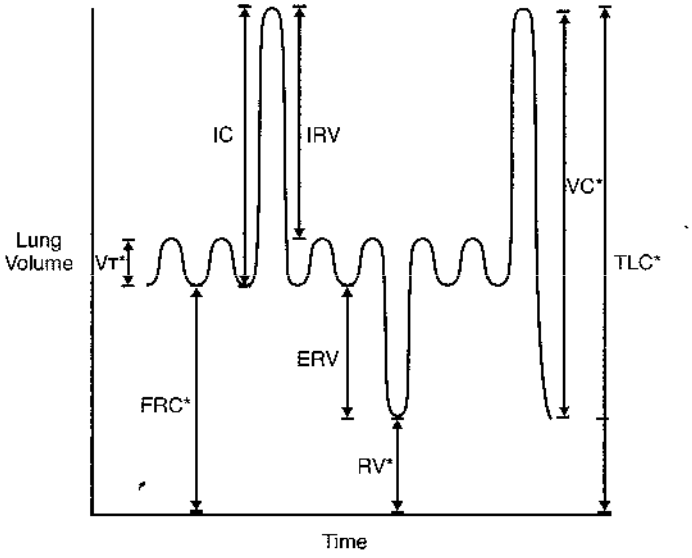


Figure VII-1-1. Lung Volumes and Capacities

Tidal volume (VT): Amount of air that enters or leaves the lung in a single respiratory cycle (500 mL).

Functional residual capacity (FRC): Volume of gas in the lungs at the end of a passive expiration; the neutral or equilibrium point for the respiratory system (2,700 mL).

Inspiratory capacity (IC): Maximal volume of gas that can be inspired from FRC (4,000 mL).

Inspiratory reserve volume (IRV): Additional amount of air that can be inhaled after a normal inspiration (3,500 mL).

Expiratory reserve volume (ERV): Additional volume that can be expired after a normal expiration (1,500 mL).

Residual volume (RV): Amount of air in the lung after a maximal expiration (1,200 mL).

Vital capacity (VC): Maximal volume that can be expired after a maximal inspiration (5,500 mL).

* **Total lung capacity (TLC):** Amount of air in the lung after a maximal inspiration (6,700 mL).

A spirometer can measure only changes in lung volume. As such, it cannot measure the residual volume or any capacity containing residual volume. TLC and FRC cannot be measured using simple spirometry; an indirect method must be used. Two common indirect methods are:

1. Helium dilution
2. Plethysmography

VENTILATION

Total Ventilation

Total ventilation is also referred to as minute volume or minute ventilation. It is the total volume of air moved in or out (usually the volume expired) of the lungs per minute.

$$\dot{V}_E = V_T \times f$$

$\dot{V}_E$ = total ventilation

V_T = tidal volume

f = respiratory rate

Normal resting values would be: $V_T = 500$ mL $\quad f = 15$

$$500 \text{ mL} \times 15/\text{min} = 7{,}500 \text{ mL/min}$$

Dead Space

Regions of the respiratory system that contain air but are not exchanging O_2 and CO_2 with blood are considered dead space.

Anatomic dead space

Airway regions that, because of inherent structure, are not capable of O_2 and CO_2 exchange with the blood. Anatomic dead space includes the conducting zone, which ends at the level of the terminal bronchioles. Significant gas exchange (O_2 and CO_2) with the blood occurs only in the alveoli.

The size of the anatomic dead space in mL is approximately equal to a person's weight in pounds. Thus a 150-lb individual has an anatomic dead space of 150 mL.

Composition of the anatomic dead space and the respiratory zone

The respiratory zone is a very constant environment. Under resting conditions, rhythmic ventilation introduces a small volume into a much larger respiratory zone. Thus, the partial pressure of gases in the alveolar compartment changes very little during normal rhythmic ventilation.

Composition at the End of Expiration (Before Inspiration)

At the end of an expiration, the anatomic dead space is filled with air that originated in the alveoli or respiratory zone. Thus, the composition of the air in the entire respiratory system is the same at this static point in the respiratory cycle. This also means that a sample of expired gas taken near the end of expiration (end tidal air) is representative of the respiratory zone. This situation is illustrated in Figure VII-1-2.

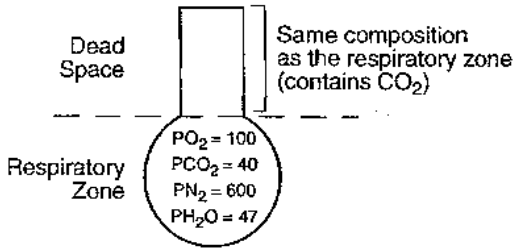


Figure VII-1-2. End of Expiration

Composition at the End of Inspiration (Before Expiration)
The first 150 mL of any inspiration fills the dead space with room air, and the first 150 mL to reach the alveoli consists of dead space air (same composition as alveolar gas). The last 150 mL of inspired air remains in the dead space. This can be considered dead-space ventilation. Beyond 150 mL, room air is added to the respiratory zone. This also means that after the first 150 mL through the remainder of inspiration, the dead space contains humidified room air. This is illustrated in Figure VII-1-3.

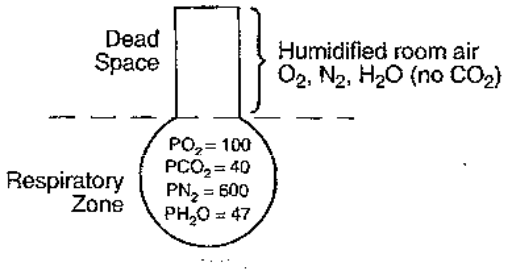


Figure VII-1-3. End of Inspiration

Alveolar dead space

Alveoli containing air but without blood flow in the surrounding capillaries.

Physiologic dead space

This is the total dead space in the lung system (anatomic dead space plus alveolar dead space).

Alveolar Ventilation

Alveolar ventilation represents the room air delivered to the respiratory zone per minute. The first 150 mL of each inspiration comes from the anatomic dead space and does not contribute to alveolar ventilation. However, every additional mL beyond 150 does contribute to alveolar ventilation.

$$\dot{V}_A = (V_T - V_D)\, f$$

$\dot{V}_A$ = alveolar ventilation
V_T = tidal volume
V_D = dead space
f = respiratory rate

$$= (500 \text{ mL} - 150 \text{ mL})\ 15 = 5250 \text{ mL/min}$$

The alveolar ventilation per inspiration is 350 mL.

Increases in the Depth of Breathing
There will be equal increases in total and alveolar ventilation per breath, since dead space volume is constant.

If the depth of breathing increases from a depth of 500 mL to a depth of 700 mL, the increase in total and alveolar ventilation would be 200 mL.

Increases in the Rate of Breathing
There will be a greater increase in total ventilation than in alveolar ventilation, because the increased rate causes increased ventilation of dead space and alveoli.

For every additional inspiration with a tidal volume of 500 mL, total ventilation would increase 500 mL, but alveolar ventilation would increase by only 350 mL (assuming dead space is 150 mL).

Problem
Given the following:

	Tidal Volume	Rate
Person A	600 mL	10/min
Person B	300 mL	20/min

Which person has the greater alveolar ventilation?

Answer: person A

Person B has rapid, shallow breathing. This person has a large component of dead space ventilation (first 150 mL of each inspiration). Even though total ventilation may be normal, alveolar ventilation is depressed. Therefore, the individual is hypoventilating.

In rapid, shallow breathing, total ventilation may be above normal, but alveolar ventilation may be below normal.

INTRODUCTION TO LUNG MECHANICS

Muscles of Respiration

Inspiration

The major muscle of inspiration is the diaphragm. Contraction of the diaphragm enlarges the vertical dimensions of the chest. Also utilized are the muscles of the chest wall. Contraction of these muscles causes the ribs to rise and thus increases the anterior-posterior dimensions of the chest.

Expiration

Under resting conditions, expiration is normally a passive process; i.e., it is due to the relaxation of the muscles of inspiration. When it is active, the muscles of the abdominal wall can be considered the main muscles of expiration. The contraction forces the diaphragm up into the chest.

Included would be external oblique, **rectus abdominal**, internal oblique, and transverse abdominal muscles.

Forces Acting on the Lung System

Units of pressure

In respiratory physiology, they are usually given as cm H_2O.

1 cm H_2O = 0.74 mm Hg (1 mm Hg = 1.36 cm H_2O)

Lung recoil and intrapleural pressure

Understanding lung mechanics mainly involves understanding the two main forces acting on the lung: lung recoil and intrapleural pressure.

Lung Recoil

- Represents forces that develop in the wall of the lung as the lung expands.
- As the lung enlarges, recoil increases; as the lung gets smaller, recoil decreases.
- Recoil, as a force, always acts to collapse the lung.

Intrapleural Pressure

- Represents the pressure in the thin film of fluid between the lung and the chest wall.
- Subatmospheric pressures (–) act as a force to expand the lung, and positive pressures (+) act as a force to collapse the lung.
- During normal restful breathing, intrapleural pressure is always subatmospheric (or negative) and thus acts as a force to expand the lung.
- When intrapleural pressure is a greater force than lung recoil, the lungs expand.
- When the recoil force is greater than that created by intrapleural pressure, lung volume will be decreasing.
- When the force of recoil and intrapleural pressure are equal and opposite, a static state exists, and lung size will be constant.

MECHANICS UNDER RESTING CONDITIONS

Before Inspiration

The glottis is open, and all respiratory muscles are relaxed (FRC). This is the neutral or equilibrium point of the respiratory system (Figure VII-1-4). Intrapleural pressure is negative at FRC because the inward elastic recoil of the lungs is opposed by the outward-directed recoil of the chest wall. The intrapleural force and recoil force are equal and opposite, and because no air is flowing through the open glottis, alveolar pressure must be zero. By convention, the atmospheric pressure is set to equal zero.

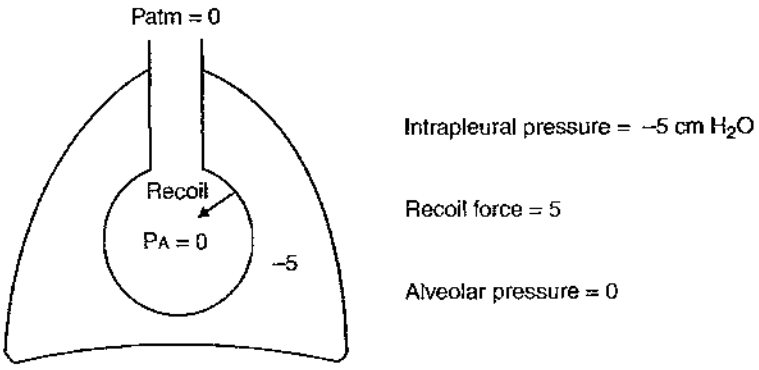


Figure VII-1-4. Lung Force Relationships at FRC

During Inspiration

1. Inspiration is induced by the contraction of the diaphragm and some accessory muscles that expand the chest wall. The net result is to make intrapleural pressure more negative.

   The greater the contraction, the greater the change in intrapleural pressure and the larger the force trying to expand the lung.

2. The expansion of the lung causes the gases in the alveoli to expand, creating a slightly negative alveolar pressure. This causes air to flow into the lung.

Figure VII-1-5 illustrates the situation at some point during inspiration.

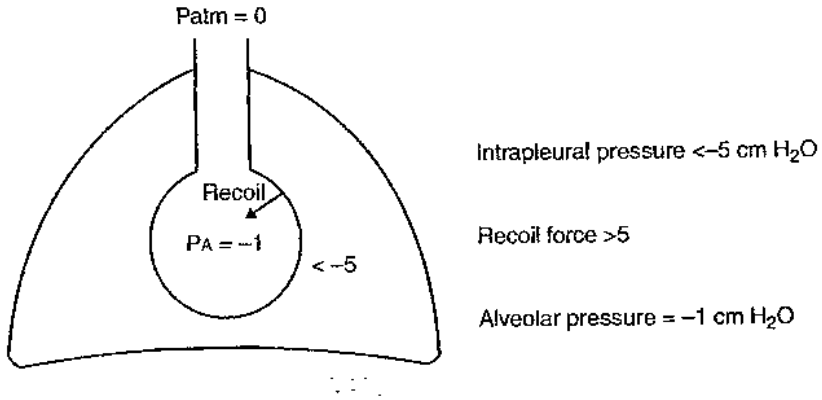


Figure VII-1-5. Lung Forces During Inspiration

End of Inspiration

1. The lung expands until the recoil force increases to equal intrapleural pressure. Once the forces are again equal and opposite, the lung is at its new larger volume.
2. The inflowing air returns alveolar pressure toward zero, and when it reaches zero, airflow stops. Under resting conditions, about 500 mL of air flows into the lung system in order to return alveolar pressure back to zero.

Figure VII-1-6 illustrates the situation at the end of a normal inspiration.

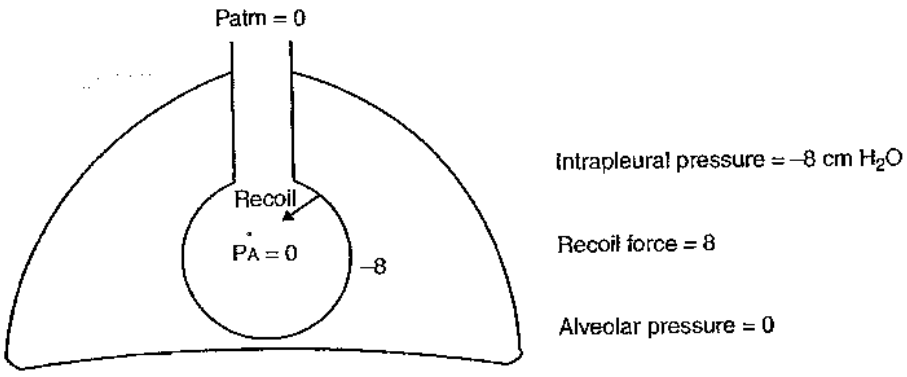
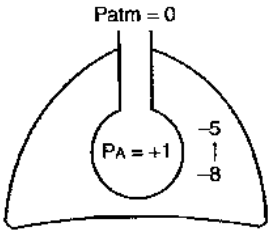


Figure VII-1-6. Lung Forces at End of Inspiration



Expiration

Expiration

1. Expiration under resting conditions is produced simply by the relaxation of the muscles of inspiration.
2. Relaxation of the muscles of inspiration causes intrapleural pressure to return to –5 cm H_2O.
3. Lung deflation begins and continues until the recoil force decreases to again equal intrapleural pressure. Once this occurs, the lung system is back to FRC.
4. Deflation of the lung compresses the gases in the alveoli, creating a slightly positive alveolar pressure. This causes air to flow out of the lungs.
5. The outflowing air returns alveolar pressure toward zero, and when it reaches zero, airflow stops.

Intrapleural pressure during a normal respiratory cycle

The intrapleural pressure during a normal respiratory cycle is illustrated in Figure VII-1-7. Under resting conditions, it is always a subatmosphere pressure.

Intraalveolar pressure during a normal respiratory cycle

The intraalveolar pressure during a normal respiratory cycle is illustrated in Figure VII-1-7. Intraalveolar pressure is slightly negative during inspiration and slightly positive during expiration. By convention, total atmospheric pressure = 0.

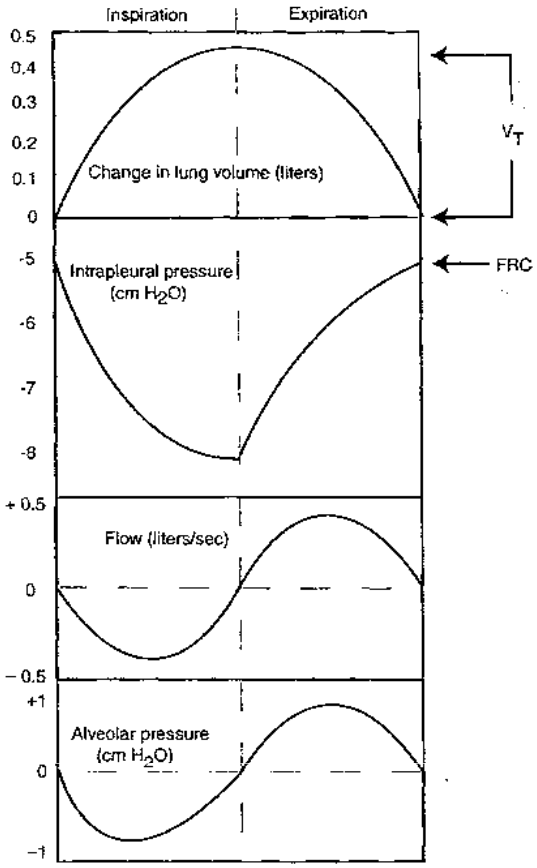


Figure VII-1-7. Essentials of Pulmonary Events During a Breath

EFFECTS OF INTRAPLEURAL PRESSURE ON PULMONARY BLOOD FLOW AND VOLUME

Inspiration

- **Intrapleural pressure becomes more negative (decreases).**
- Systemic venous return and right ventricular output are increased.
- An increase in the output of the right ventricle will delay the closing of the pulmonic valves and may result in a splitting of the second heart sound.
- Pulmonary vessels expand, and the volume of blood in the pulmonary circuit increases.
- Venous returns to the left heart, and the output of the left ventricle is decreased, causing decreased systemic arterial pressure.
- Expansion of the right atrium and the ensuing drop in blood pressure cause a reflex increase in heart rate (sinus arrhythmia).

Expiration

- **Intrapleural pressure becomes more positive (increases).**
- Systemic venous return and output of the right ventricle are decreased.
- Pulmonary vessels are compressed, and the volume of blood in the pulmonary circuit is decreased.
- The return of blood and output of the left ventricle are increased, causing increased systemic arterial pressure.
- The right atrium is compressed, and the blood pressure is increased, causing a reflex decrease in heart rate.
- A Valsalva maneuver will also increase intrapleural pressure and central venous pressure and decrease venous return.

POSITIVE-PRESSURE RESPIRATION

Assisted Control Mode Ventilation (ACMV)

Inspiratory cycle initiated by patient or automatically if no signal is detected within a specified time window.

Positive End-Expiratory Pressure (PEEP)

Volume cycled rather than pressure or timed cycled is the most common.

Controlled mode—machine-triggered

Assist mode—inspiratory cycle initiated by the patient

CPAP—continuous airway pressure in spontaneous breathing patients

PEEP (positive end-expiratory pressure)—positive pressure is applied at the end of the expiratory cycle to decrease alveolar collapse. Small alveoli have a strong tendency to collapse, creating regions of atelectasis. The larger alveoli are also better ventilated, and supplementary oxygen is more effective at maintaining a normal arterial PO_2. One downside to positive pressure ventilation and accentuated by PEEP is a decrease in venous return and cardiac output. Positive pressure ventilation and the addition of PEEP are illustrated below.

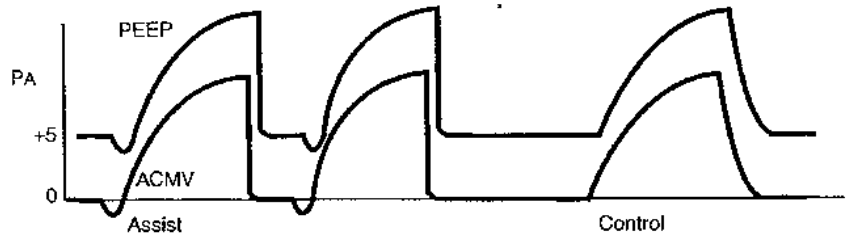


Figure VII-1-8. Positive-Pressure Ventilation

PNEUMOTHORAX

The following changes would occur with the development of a simple pneumothorax:

- Intrapleural pressure increases from a mean at –5 cm H_2O to equal atmospheric pressure.
- Lung recoil decreases to zero as the lung collapses.
- Chest wall expands. At FRC, the chest wall is under a slight tension directed outward. It is this tendency for the chest wall to spring out and the opposed force of recoil that creates the intrapleural pressure of –5 cm H_2O.

In some cases, the opening of the lung to the pleural space may function as a valve allowing the air to enter the pleural space but not to leave.

Strong inspiratory efforts promote the entry of air into the pleural space, but during expiration, the valve closes and positive pressures are created in the chest cavity. Ventilation decreases but the positive pressures also decrease venous return and cardiac output.

Tension pneumothorax most commonly develops in patients on a positive-pressure ventilator.

LUNG COMPLIANCE

Figure VII-1-9 represents a static isolated lung inflation curve.

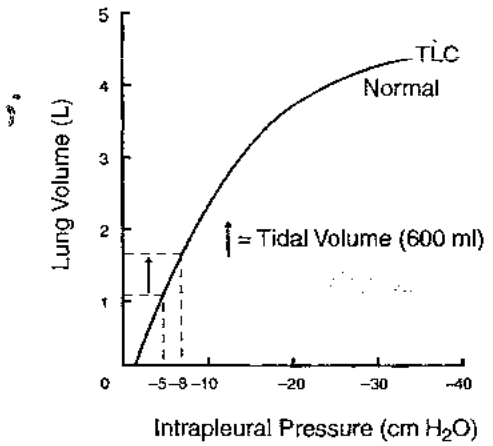


Figure VII-1-9. Lung Inflation Curve

Lung compliance is the change in lung volume (tidal volume) divided by the change in surrounding pressure. This is stated in the following formula:

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Problem

Tidal volume = 0.6 liters

Intrapleural pressure before inspiration = -5 cm H_2O

Intrapleural pressure after inspiration = -8 cm H_2O

$$\text{Lung compliance} = \frac{0.6 \text{ liters}}{3 \text{ cm } H_2O} = 0.200 \text{ liters/cm } H_2O$$

The preceding calculation simply means that for every 1 cm H_2O surrounding pressure changes, 200 mL of air flows in or out of the respiratory system. It flows into the system if surrounding pressure becomes more negative (e.g., -5 to -6 cm H_2O) or out of the system if surrounding pressure becomes more positive (e.g., -5 to -4 cm H_2O).

Increased compliance means more air will flow for a given change in pressure.

Reduced compliance means less air will flow for a given change in pressure.

In the preceding curve, although the slope is changing during inflation, its value at any point is the lung's compliance. It is the relationship between the change in lung volume (tidal volume) and the change in intrapleural or surrounding pressure.

The steeper the line, the more compliant the lungs. Restful breathing works on the steepest, most compliant part of the curve. With a deep inspiration, the lung will move toward the flatter part of the curve, and thus it will have reduced compliance. At total lung capacity (TLC), lung compliance is reduced compared with FRC.

Figure VII-1-10 shows states in which lung compliance changes.

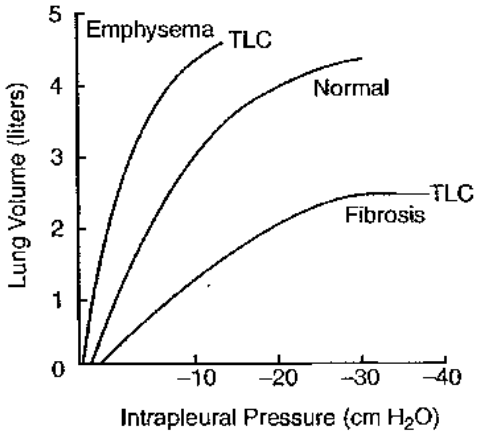


Figure VII-1-10. Lung Compliance

Increased lung compliance also occurs with aging and with a saline-filled lung.

In summary: Compliance is an index of the effort required to expand the lungs (to overcome recoil). It does not relate to airway resistance. Also, the compliance will change as the lungs are inflated because the curve is not a straight line. Very compliant lungs (easy to inflate) have low recoil. Stiff lungs (difficult to inflate) have a large recoil force.

Components of Lung Recoil

Lung recoil has two components:

1. The tissue itself; more specifically, the collagen and elastin fibers of the lung.

   The larger the lung, the greater the stretch of the tissue and the greater the recoil force.

2. The surface tension forces in the fluid lining the alveoli. Surface tension forces are created whenever there is a liquid–air interface (Figure VII-1-11).

   Surface tension forces tend to reduce the area of the surface and generate a pressure. In the alveoli, they act to collapse the alveoli; therefore, these forces contribute to lung recoil.

   Surface tension forces are the greatest component of lung recoil.

   The relationship between the surface tension and the pressure inside a bubble is given by the law of LaPlace.

$$P \propto \frac{T}{r}$$

P = pressure

T = tension

r = radius

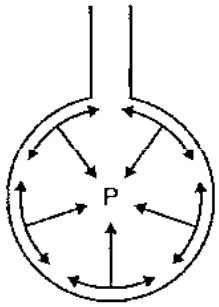


Figure VII-1-11. Surface Tension

If wall tension is the same in two bubbles, the smaller bubble will have the greater pressure.

Although the situation is more complex in the lung, it follows that small alveoli tend to be unstable. They have a great tendency to empty into larger alveoli and collapse (creating regions of atelectasis). This is illustrated in Figure VII-1-12. Collapsed alveoli are difficult to reinflate.

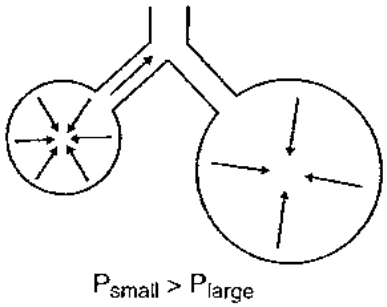


Figure VII-1-12. Atelectasis

If the alveoli were lined with a simple electrolyte solution, lung recoil would be so great that lungs theoretically should not be able to inflate. This is prevented by a chemical, surfactant, in the fluid lining a normal lung.

Surfactant has three main functions:

1. It lowers surface tension forces in the alveoli. In other words, surfactant lowers lung recoil and increases compliance.
2. It lowers surface tension forces more in small alveoli than in large alveoli. This promotes stability among alveoli of different sizes by decreasing the tendency of small alveoli to collapse (decreases the tendency to develop atelectasis).
3. It reduces capillary filtration forces and thus reduces the tendency to develop pulmonary edema. A negative intrathoracic pressure is a force promoting capillary filtration. Low recoil means an intrapleural pressure closer to atmospheric, and under these conditions it is not a significant force promoting filtration.

Respiratory Distress Syndrome (RDS)

Infant respiratory distress syndrome (hyaline membrane disease): deficiency of surfactant

Adult respiratory distress syndrome (ARDS): acute lung injury via the following:

- Bloodstream—Sepsis—develops from injury to the pulmonary capillary endothelium, leading to interstitial edema and increased lymph flow. This leads to injury and increased permeability of the alveolar epithelium and alveolar edema. The protein seepage into the alveoli reduces the effectiveness of surfactant. Neutrophils have been implicated in the progressive lung injury from sepsis.
- Airway—Gastric aspirations—direct acute injury to the lung epithelium increases permeability of the epithelium followed by edema.

Curve A in Figure VII-1-13 represents respiratory distress syndrome. The curve is shifted to the right, and it is a flatter curve (lung stiffer). Curve B represents atelectasis.

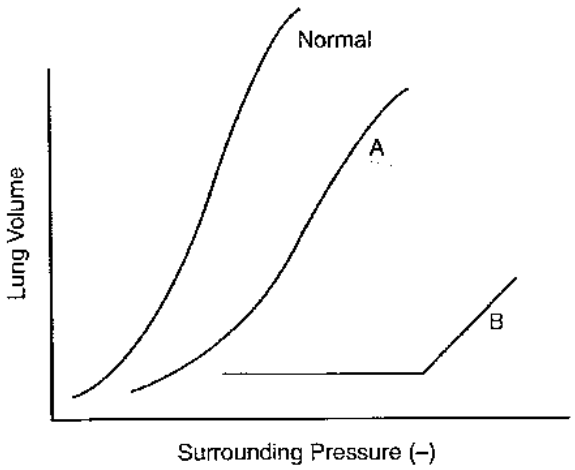


Figure VII-1-13. Deficiency of Surfactant

The symptoms include:

1. Increased lung recoil and decreased lung compliance.

   At a given lung volume, intrapleural pressure will be more negative.

   A greater change in intrapleural pressure is required to inflate the lungs.

2. Atelectasis

   There is a greater tendency for small alveoli to collapse. Once collapse occurs, it is difficult to reinflate these alveoli.

   This is illustrated in curve B in Figure VII-1-13. Here a very negative intrapleural pressure (inspiratory effort) is required to reinflate the alveoli.

3. Pulmonary edema

   Because a deficiency of surfactant increases recoil, a more negative intrathoracic pressure is required to maintain a given lung volume.

   Very negative intrapleural pressures represent a large force promoting capillary filtration.

AIRWAY RESISTANCE

Radius of an Airway

$$\text{Resistance} \propto \frac{1}{\text{radius}^4}$$

In the branching airway system of the lungs, it is the first and second bronchi that represent most of the airway resistance.

Parasympathetic nerve stimulation produces bronchoconstriction.

Circulating catecholamines produce bronchodilation.

Mechanical Effect of Lung Volume

Figure VII-1-14 demonstrates the mechanical effect of lung volume.

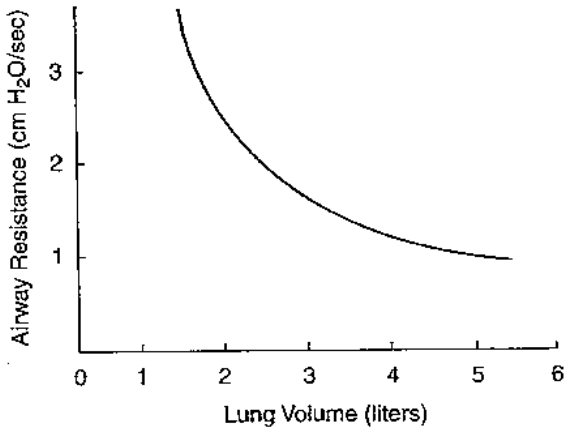


Figure VII-1-14. Airway Resistance

During inspiration, intrapleural pressure is decreasing, which produces greater transverse stretch that opens the airways. Consequently, airway resistance decreases during inspiration.

The more negative the intrapleural pressure, the lower the resistance of the airways.

PULMONARY FUNCTION TESTING

Vital Capacity (VC)

The VC is the maximum volume of air that an individual can move in a single breath. The most useful assessment of the VC is to expire as quickly and forcefully as possible, i.e., a "timed" or forced vital capacity (FVC). During the FVC maneuver, the volume of air exhaled in the first second is called the forced expiratory volume in 1 sec (FEV_1). This is illustrated in Figure VII-1-15. Please note that Figure VII-1-15 and the following figures differ from the output of a spirometer, because they show actual lung volumes (including residual volume) instead of showing only changes of volume.

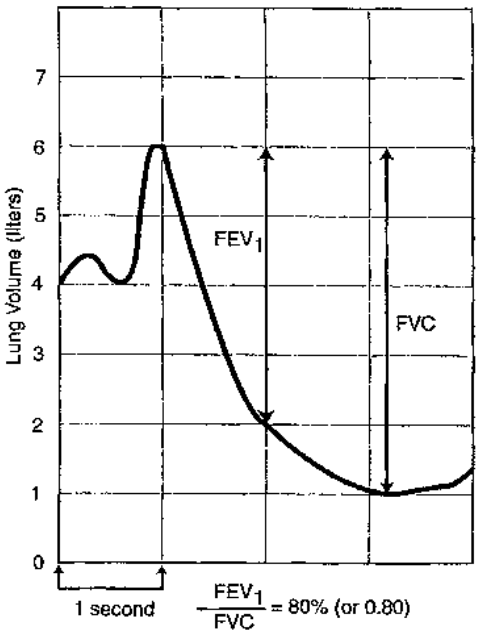


Figure VII-1-15, Forced Expiratory Test

Normal people can exhale only 80% of their VC in 1 second because during a forced expiration, intrapleural pressure becomes positive and the airways are compressed. Compression of the airways limits expiratory flow rates. This compression is called "dynamic compression of the airways." Maximum expiratory flow rates are "effort independent" (Figure VII-1-16).

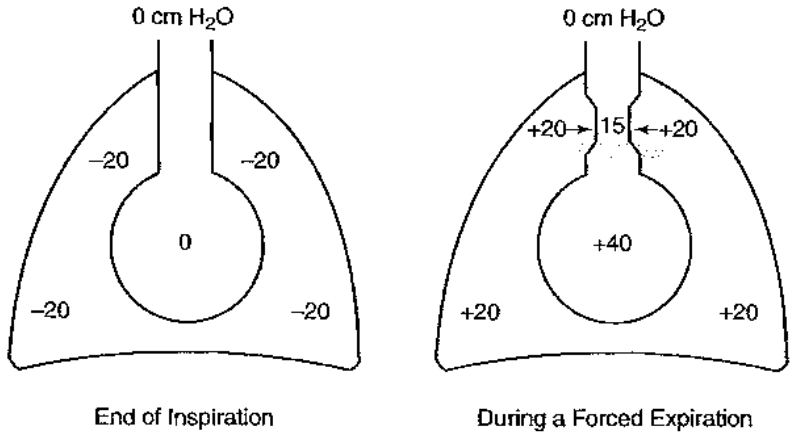


Figure VII-1-16. Dynamic Airway Compression

Obstructive Versus Restrictive Patterns

The following figures (Figures VII-1-17 and VII-1-18) demonstrate a standard pulmonary function test, the measurement of FVC, FEV_1, and FEV_1/FVC.

Obstructive pulmonary disease

Obstructive disease is characterized by an increase in airway resistance that is measured as a decrease in expiratory flow rates. Examples are chronic bronchitis, asthma, and emphysema.

Obstructive pattern

Total lung capacity (TLC) is normal or larger than normal, but during a maximal forced expiration from TLC, a smaller than normal volume is slowly expired.

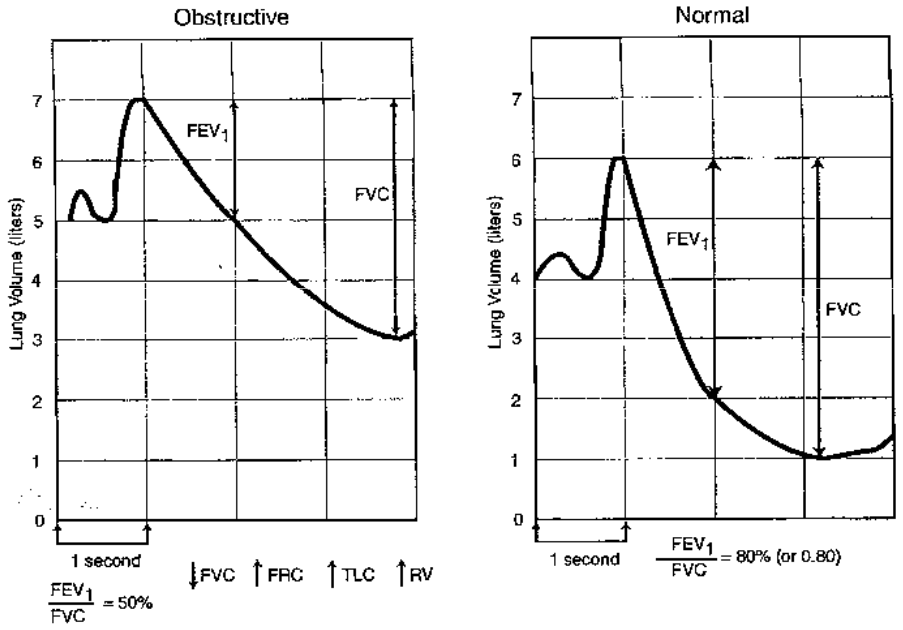


Figure VII-1-17. Obstructive Pattern

Restrictive pulmonary disease

Restrictive pulmonary disease is characterized by an increase in elastic recoil—a decrease in lung compliance—which is measured as a decrease in all lung volumes. Reduced vital capacity with low lung volumes are the indicators of restrictive pulmonary diseases.

Restrictive pattern

TLC is smaller than normal, but during a maximal forced expiration from TLC, the smaller volume is expired quickly and more completely than in a normal pattern; therefore, even though FEV_1 is also reduced, the FEV_1/FVC is often increased. However, the critical distinction is low FVC with low FRC and RV.

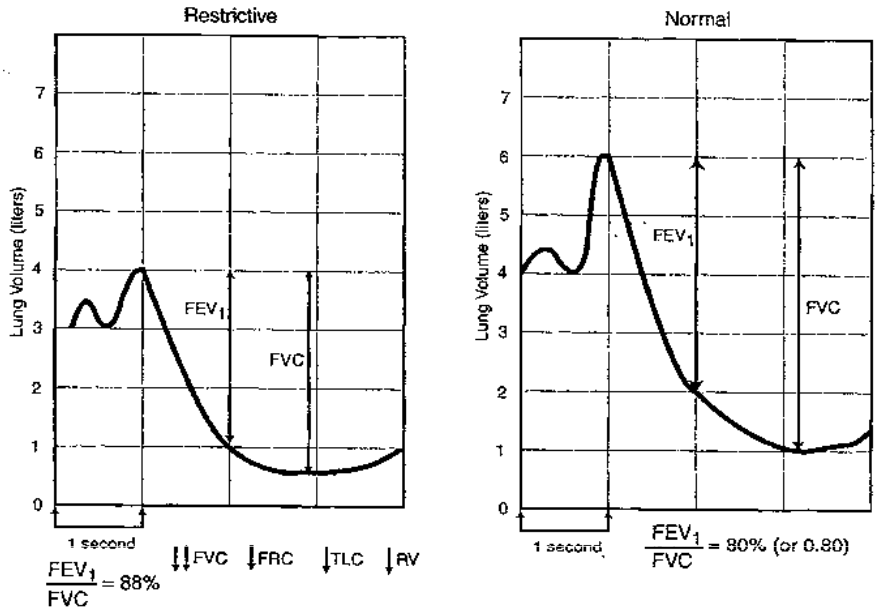


Figure VII-1-18. Restrictive Pattern

Table VII-1-1. Summary of Obstructive Versus Restrictive Pattern

Variable	Obstructive Pattern e.g., Emphysema	Restrictive Pattern e.g., Fibrosis
TLC	↑	↓↓
FEV_1	↓↓	↓
FVC	↓	↓↓
FEV_1/FVC	↓	↑ or normal
Peak flow	↓	↓
FRC	↑	↓
RV	↑	↓

FVC always decreases when pulmonary function is compromised.

A decrease in FEV_1/FVC ratio is evidence of an obstructive pattern. A normal or increased FEV_1/FVC ratio is evidence of a restrictive pattern.

Flow–Volume Loops

The instantaneous relationship between flow (liters/sec) and lung volume is useful in determining whether obstructive or restrictive lung disease is present. In the loop shown in Figure VII-1-19, expiration starts at total lung capacity and continues to residual volume.

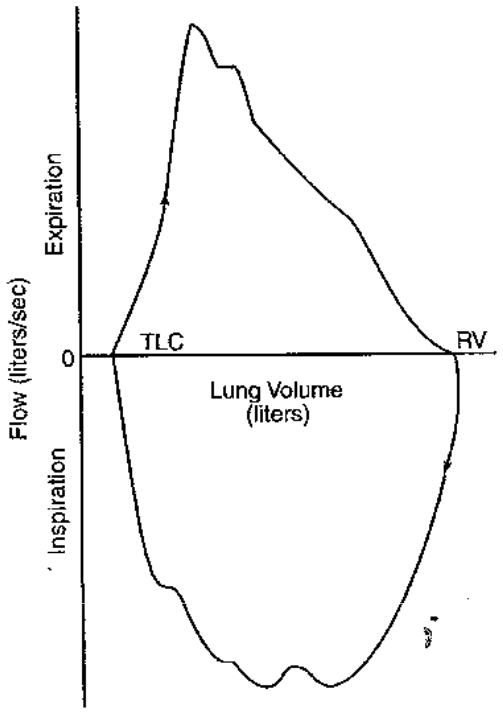


Figure VII-1-19. Flow–Volume Loop

Loops found in obstructive and restrictive disease are shown in Figure VII-1-20.

Obstructive disease

In obstructive disease, the flow–volume loop begins and ends at abnormally high lung volumes, and the expiratory flow rates are lower than normal.

Restrictive disease

In restrictive disease, the flow–volume loop begins and ends at unusually low lung volumes. When expiratory flow rates are compared at specific lung volumes, the rates in restrictive disease are somewhat greater than normal.

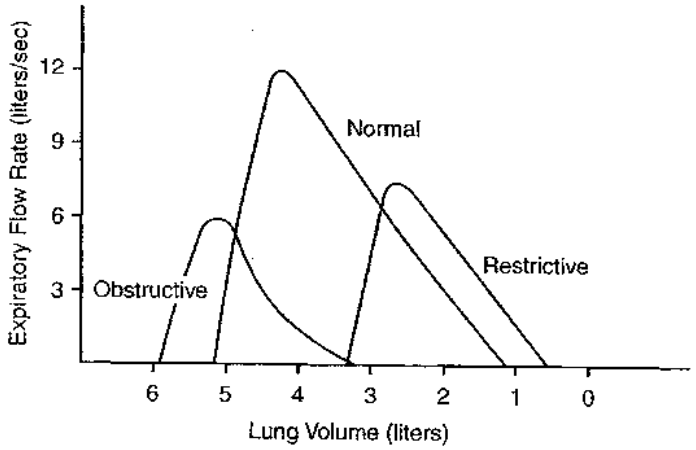


Figure VII-1-20. Forced Expiratory Flow–Volume Loop

Chapter Summary

* Functional residual capacity is the neutral or equilibrium point of the respiratory system. Residual volume is the air remaining in the respiratory system after a maximal expiration. Vital capacity is the difference between total lung capacity and residual volume.
* Dead space is air in the respiratory system that is not exchanging gas with capillary blood.
* The first 150 mL of an inspiration fills the anatomical dead space with room air. This volume contributes to total but not alveolar ventilation. Alveolar ventilation represents the inspired volume beyond 150 mL. It is the inspired air that actually reaches the respiratory zone.
* During restful breathing, intrapleural pressure is always negative. It becomes more negative during inspiration and more positive during expiration. Alveolar pressure is slightly negative during inspiration and slightly positive during expiration.
* Compliant lungs are easy to inflate and possess low recoil. Noncompliant or stiff lungs are difficult to inflate and have a large recoil force.
* The main component of lung recoil represents the surface tension forces of the fluid lining the alveoli. Surfactant reduces surface tension forces.
* A deficiency of surfactant reduces lung compliance and promotes atelectasis and the development of pulmonary edema.
* A maximal expiration is associated with a partial collapse of the large airways, which increases resistance and limits the maximum flow rate.
* An obstructive pattern is often associated with large lung volumes (TLC), but a small volume is expired slowly.
* A restrictive pattern is associated with reduced lung volumes (TLC), but the small volume is often expired rapidly.

Alveolar–Blood Gas Exchange

THE NORMAL LUNG

Introduction

Partial pressure of a gas in ambient air

Patm = atmospheric pressure; Pgas = partial pressure of a gas; Fgas = concentration of a gas

$P_{gas} = F_{gas} \times P_{atm}$

By convention, the partial pressure of the gas is expressed in terms of its dry gas concentration.

Example: The P_{O_2} in ambient air: $P_{O_2} = 0.21 \times 760 = 160$ mm Hg

Partial pressure of a gas in inspired air

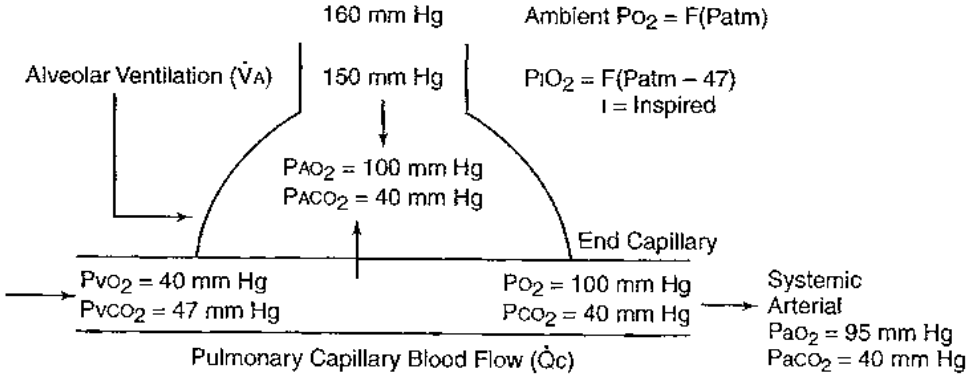
Inspired air is defined as air that has been inhaled, warmed to 37°C, and completely humidified. The partial pressure of H_2O is dependent only on temperature and at 37°C is 47 mm Hg. Humidifying the air reduces the partial pressure of the other gases present.

Pigas = partial pressure of inspired gas; P_{H_2O} = partial pressure of H_2O vapor

$P_{Igas} = F_{gas}(P_{atm} - P_{H_2O})$

Example: The P_{O_2} of inspired air: $P_{IO_2} = 0.21(760 - 47) = 150$ mm Hg

Figure VII-2-1 shows the pressures of oxygen and carbon dioxide in the alveolar, pulmonary end capillary, and systemic arterial blood.



A = alveolar, a = systemic arterial

Figure VII-2-1. Pulmonary Capillary Gases

Under normal conditions, the PO_2 and PCO_2 in the alveolar compartment and pulmonary end capillary blood are the same. There will be a slight change ($PO_2 \downarrow$) between the end capillary compartment and the systemic arterial blood because of a small but normal shunt through the lungs.

Alveolar–systemic arterial differences (usually PO_2) = A – a. This difference often provides information about the cause of a hypoxemia. There is a small difference normally because of a small amount of shunting through the lungs (5–10 mm Hg). The difference will increase in certain specific pulmonary system problems.

FACTORS AFFECTING ALVEOLAR PCO_2

Only two factors affect alveolar PCO_2. They are metabolic rate and alveolar ventilation, as shown in the following equation.

$$PACO_2 \propto \frac{\text{metabolic } CO_2 \text{ production}}{\text{alveolar ventilation}}$$

At rest, unless there is fever or hypothermia, CO_2 production is relatively constant; so you can use changes of $PACO_2$ to evaluate alveolar ventilation.

Alveolar Ventilation

There is an inverse relationship between $PACO_2$ and alveolar ventilation. This is the main factor affecting alveolar PCO_2. Therefore, if ventilation increases, $PACO_2$ decreases; if ventilation decreases, $PACO_2$ increases.

Hyperventilation

During hyperventilation, there is an inappropriately elevated level of alveolar ventilation, and $PACO_2$ is depressed.

If $\dot{V}A$ is doubled, then $PACO_2$ is decreased by half.

e.g., $PACO_2$ = 40 mm Hg

2 × $\dot{V}A$; $PACO_2$ = 20 mm Hg

Hypoventilation

During hypoventilation, there is an inappropriately depressed level of alveolar ventilation, and $PACO_2$ is elevated.

If $\dot{V}A$ is halved, then $PACO_2$ is doubled.

e.g., $PACO_2$ = 40 mm Hg

1/2 $\dot{V}A$; $PACO_2$ = 80 mm Hg

Metabolic Rate

There is a direct relationship between alveolar PCO_2 and body metabolism. For $PACO_2$ to remain constant, changes in body metabolism must be matched with equivalent changes in alveolar ventilation.

If $\dot{V}A$ matches metabolism, then $PACO_2$ remains constant.

For example, during exercise, if body metabolism doubles, then $\dot{V}A$ must double if $PACO_2$ is to remain constant.

If body temperature decreases and there is no change in ventilation, $PACO_2$ will decrease, and the individual can be considered to be hyperventilating.

FACTORS AFFECTING ALVEOLAR PO_2

The Alveolar Gas Equation

The alveolar gas equation includes all the factors that can affect alveolar PO_2.

$$PAO_2 = (Patm - 47)FiO_2 - \frac{PACO_2}{R}$$

Practical application of the equation includes differential diagnosis of hypoxemia by evaluating the alveolar arterial (A–a) gradient of oxygen.

Three important factors can affect PAO_2:

Patm = atmospheric pressure, at sea level 760 mm Hg

An increase in atmospheric pressure will increase alveolar PO_2, and a decrease (high altitude) will decrease alveolar PO_2.

FiO_2 = fractional concentration of oxygen, room air 0.21

An increase in inspired oxygen concentration will increase alveolar PO_2.

$PACO_2$ = alveolar pressure of carbon dioxide, normally 40 mm Hg

An increase in alveolar PCO_2 will decrease alveolar PO_2, and a decrease will increase alveolar PO_2. For most purposes, you can use arterial carbon dioxide ($PACO_2$) in the calculation.

The fourth variable is R. It varies from 0.8 to 1.0.

$$R = \text{respiratory exchange ratio} = \frac{CO_2 \text{ produced mL/min}}{O_2 \text{ consumed mL/min}}; \text{ normally } 0.8$$

Example: person breathing room air at sea level

$$PAO_2 = (760 - 47)\ 0.21 - 40/0.8 = 100 \text{ mm Hg}$$

The Effect of $PACO_2$ on PAO_2

PIO_2 = P inspired O_2, i.e., the PO_2 in the conducting airways during inspiration

Because $PACO_2$ affects alveolar PO_2, hyperventilation and hypoventilation also affect PAO_2.

Hyperventilation (e.g., $PACO_2$ = 20 mm Hg)

$PAO_2 = PIO_2 - PACO_2$ (assume R = 1)

normal = 150 – 40 = 110 mm Hg

hyperventilation = 150 – 20 = 130 mm Hg

Hypoventilation (e.g., $PACO_2 = 80$ mm Hg)

normal = 150 – 40 = 110 mm Hg

hypoventilation = 150 – 80 = 70 mm Hg

ALVEOLAR–BLOOD GAS TRANSFER: FICK LAW OF DIFFUSION

Simple diffusion is the process of gas exchange between the alveolar compartment and pulmonary capillary blood. Thus, those factors that affect the rate of diffusion also affect the rate of exchange of O_2 and CO_2 across alveolar membranes. (An additional point to remember is that each gas diffuses independently.)

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2)$$ **$\dot{V}$gas is the rate of gas diffusion**

Two structural factors and two gas factors affect the rate of diffusion.

Structural Features That Affect the Rate of Diffusion

A = surface area for exchange, ↓ in emphysema, ↑ in exercise

T = thickness of the membranes between alveolar gas and capillary blood, ↑ in fibrosis and many other restrictive diseases

A structural problem in the lungs is any situation in which there is a loss of surface area and/or an increase in the thickness of the membrane system between the alveolar air and the pulmonary capillary blood. In all cases, the rate of oxygen and carbon dioxide diffusion decreases. The greater the structural problem, the greater the effect on diffusion rate.

Factors That Are Specific to Each Gas Present

D (diffusion constant) = main factor is solubility

The only clinically significant feature of D is solubility. The more soluble the gas, the faster it will diffuse across the membranes. CO_2 is the most soluble gas with which we will be dealing. The great solubility of CO_2 is the main reason why it diffuses faster across the alveolar membranes than O_2.

Gradient across the membrane

$(P_1 - P_2)$: This is the gas partial pressure difference across the alveolar membrane. The greater the partial pressure difference, the greater the rate of diffusion.

Under resting conditions, when blood first enters the pulmonary capillary, the gradient for O_2 is:

100 – 40 = 60 mm Hg

An increase in the PO_2 gradient across the lung membranes will compensate for a structural problem. If supplemental O_2 is administered, alveolar PO_2 will increase, along with the gradient. This increased gradient will return the rate of O_2 diffusion toward normal. The greater the structural problem, the greater the gradient necessary for a normal rate of O_2 diffusion.

The gradient for CO_2 is 47 – 40 = 7 mm Hg.

Even though the gradient for CO_2 is less than for O_2, CO_2 still diffuses faster because of its greater solubility.

DIFFUSION CAPACITY OF THE LUNG (DLCO)

There are two terms to describe the dynamics of the transfer of individual substances between the interstitium and the capillary:

- If the substance equilibrates between the capillary and the interstitium, it is said to be in a perfusion-limited situation.
- If the substance does not equilibrate between the capillary and the interstitium, it is said to be in a diffusion-limited situation.

Carbon monoxide is a unique gas in that it can never equilibrate between the alveolar air and the capillary blood. In other words, it is always in a diffusion-limited situation. This is taken advantage of clinically, and the measurement of the uptake of CO in mL/min/mm Hg is referred to as the diffusion capacity of the lung. It is an index of the lung's structural features.

Carbon Monoxide: A Gas that is Always Diffusion Limited

Carbon monoxide has an extremely high affinity for hemoglobin. When it is present in the blood, essentially all is combined with hemoglobin, and the amount dissolved in the plasma is zero (therefore, partial pressure in the plasma is zero). Thus, the alveolar partial pressure is the gradient ($P_1 - P_2$). At a constant and known alveolar partial pressure, the uptake of carbon monoxide depends only on the structural features of the lung, as illustrated in Figure VII-2-2.

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2)$$

$$\dot{V}CO = \frac{A}{T} \times D \times P_ACO$$

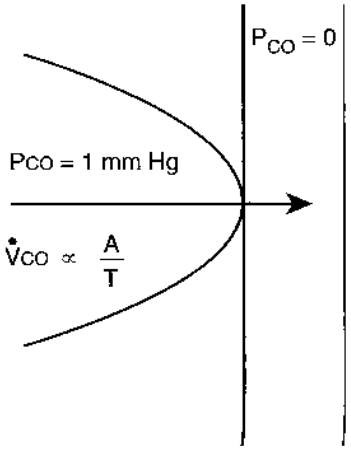


Figure VII-2-2. Carbon Monoxide

In a young individual with normal lung surface area (A) and thickness (T), a 1-mm Hg gradient of carbon monoxide will produce an uptake of 25 mL/min.

This measured uptake of carbon monoxide is called the diffusion capacity of the lung (DL; mL/min/mm Hg). It is an index of overall surface area and membrane thickness. With a structural problem, it correlates with the extent of lung damage and is particularly useful when measured serially over time.

DL (rate of CO diffusion) decreases in emphysema and fibrosis but increases during exercise.

Chapter Summary

* In a normal resting individual at sea level, the partial pressures of oxygen and carbon dioxide are not significantly different among the alveolar, pulmonary end capillary, and systemic arterial compartments (PO_2 = 100 mm Hg and PCO_2 = 40 mm Hg).
* Only two factors affect alveolar PCO_2: body metabolism and alveolar ventilation. If body metabolism is constant, there is an inverse relationship between alveolar ventilation and alveolar PCO_2.
* Three important factors affect alveolar PO_2: atmospheric pressure, oxygen concentration in the inspired air, and alveolar PCO_2.
* A change in alveolar PCO_2 will cause a change in alveolar PO_2. They will change in opposite directions approximately the same amount in mm Hg.
* Two structural factors and two gas factors affect the rate of gas diffusion across lung membranes.
* Diffusion rate is directly proportional to membrane surface area and inversely proportional to membrane thickness.
* The partial pressure gradient is the driving force for diffusion.
* Because CO_2 is an extremely soluble gas, it diffuses across the lung membranes faster than oxygen even though it has a small gradient.
* Supplemental oxygen raises the oxygen gradient and can compensate for a structural problem.
* The diffusion capacity of the lung is an index of the overall surface area and membrane thickness. It is measured as the uptake of CO from the alveolar air to the blood in mL/min/mm Hg.

Transport of O_2 and CO_2 and the Regulation of Ventilation

TRANSPORT OF OXYGEN

Units of Oxygen Content

Oxygen content = the concentration of oxygen in the blood, e.g., arterial blood = 20 volumes % = 20 volumes of oxygen per 100 volumes of blood = 20 mL of oxygen per 100 mL of blood = 0.2 mL of oxygen per mL of blood.

Dissolved Oxygen

Oxygen is not a very soluble gas in plasma; very little is present in this form. Thus, only a very small amount of oxygen is delivered to the capillaries as dissolved oxygen.

However, there is a direct linear relationship between PO_2 and dissolved oxygen (Figure VII-3-1). When the PO_2 is 100 mm Hg, 0.3 mL O_2 is dissolved in each 100 mL of blood (0.3 vol%).

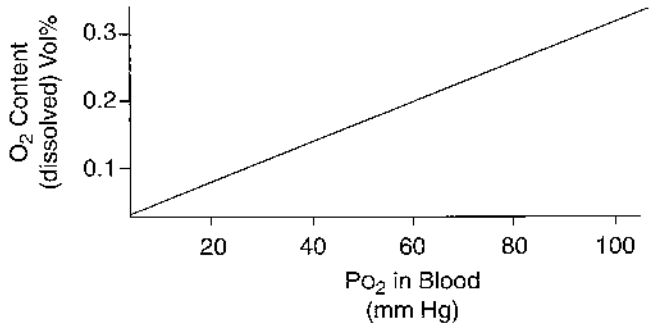


Figure VII-3-1. Dissolved Oxygen in Plasma

Also PO_2 is a force created by dissolved oxygen, which acts to keep oxygen on hemoglobin (Hb).

Whether oxygen is attached to a site on Hb depends on the affinity of that site for oxygen and the PO_2. The greater the affinity of a site for oxygen, the lower the required PO_2 to keep the oxygen attached.

Oxyhemoglobin

Each Hb molecule can attach and carry up to four oxygen molecules. Binding sites on Hb have different affinities for oxygen. Also, the affinity of a site can and does change as oxygen is loaded or unloaded from the Hb molecule and as the chemical composition of the plasma changes.

Site 4 – O_2 attached when the minimal $PO_2 \cong 100$ mm Hg	systemic arterial blood = 97% saturated
Site 3 – O_2 attached when the minimal $PO_2 \cong 40$ mm Hg	systemic venous blood = 75% saturated (resting state)
Site 2 – O_2 attached when the minimal $PO_2 \cong 26$ mm Hg	P_{50} for arterial blood. P_{50} is the PO_2 required for 50% saturation

Site 1 – O_2 usually remains attached under physiologic conditions. Under physiologic conditions, only sites 2, 3, and 4 need to be considered.

Most of the oxygen in systemic arterial blood is oxygen attached to Hb. The only significant form in which oxygen is delivered to systemic capillaries is oxygen bound to Hb.

Hemoglobin O_2 Content

The number of mL of oxygen carried in each 100 mL of blood in combination with Hb depends on the Hb concentration [Hb]. Each gram of Hb can combine with 1.34 mL of O_2. If the [Hb] is 15 g/100 mL (15 g%), then the maximal amount of O_2 per 100 mL (100% saturation) in combination with Hb is:

$1.34([Hb]) = 1.34(15) = 20$ mL O_2/100 mL blood = 20 vol%. This volume represents the "carrying capacity" of the blood.

The Hb in systemic arterial blood is about 97% saturated with oxygen, which means slightly less than 20 vol% is carried by Hb.

When blood passes through a systemic capillary, it is the dissolved oxygen that diffuses to the tissues. However, if dissolved oxygen decreases, PO_2 also decreases, and there is less force to keep oxygen attached to Hb. Oxygen comes off Hb and dissolves in the plasma to maintain the flow of oxygen to the tissues.

Hyperventilation or supplementing the inspired air with additional oxygen in a normal individual can significantly increase the PaO_2 but with little effect on total oxygen content. For example:

	Dissolved O_2	HbO_2	Total O_2 Content
If PaO_2 = 100 mm Hg	0.3	≅ 19.4	≅ 19.7 vol%
If PaO_2 = 130 mm Hg (hyperventilation)	0.4	≅ 19.4	≅ 19.8 vol%

Oxygen–Hb Dissociation Curves

Figure VII-3-2 represents three major points on the oxygen–hemoglobin dissociation curve. The numbered sites refer to the hemoglobin site numbers discussed just previously.

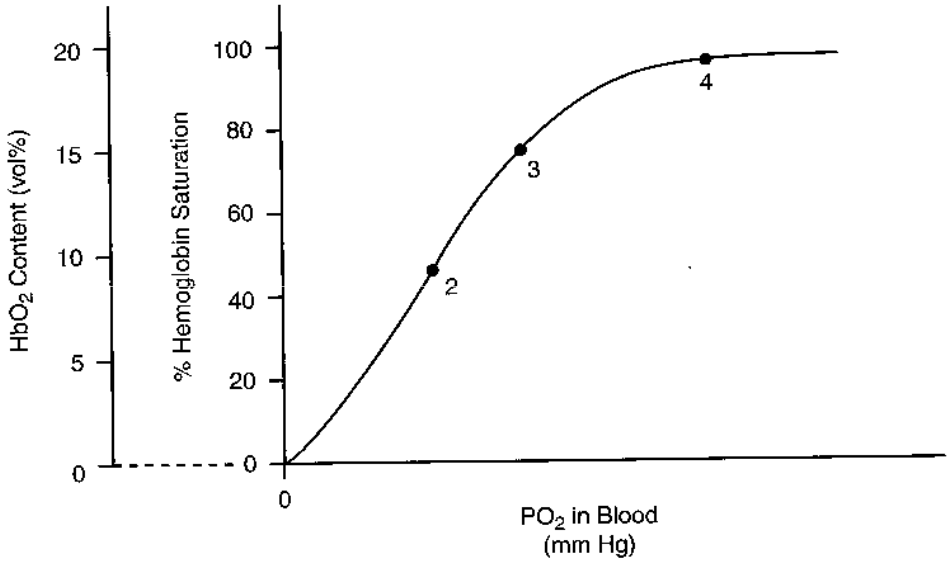


Figure VII-3-2. Oxygen–Hb Dissociation Curves

Shifting the curve

The following will shift the curve to the right: increased CO_2 (Bohr effect), increased hydrogen ion (decrease pH), increased temperature, increased 2,3-diphosphoglycerate (2,3-DPG).

In each case, the result can be explained as a loss of affinity of the Hb molecule for oxygen. However, carrying capacity is not changed, and systemic arterial blood at a PO_2 of 100 mm Hg will still be close to 100% saturation.

The opposite chemical changes will shift the curve to the left.

Figure VII-3-3 shows the result of a shift in the O_2–Hb dissociation curve. Note that only points on the steep part of the curve are affected.

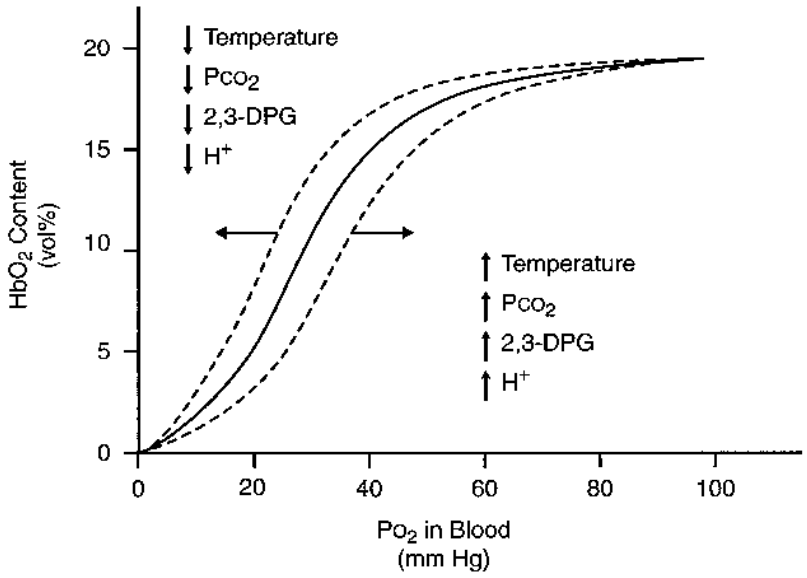


Figure VII-3-3. Shifts in Hb-O_2 Dissociation Curve

Shift to the right:
Easier for tissues to extract oxygen
Steep part of curve, O_2 content decreased
P_{50} increased

Shift to the left:
More difficult for tissues to extract oxygen
Steep part of curve, O_2 content increased
P_{50} decreased

Stored blood loses 2,3-diphosphoglycerate, causing a shift to the left. Fetal hemoglobin is also shifted to the left.

Hb Concentration Effects

Anemia

Characterized by a reduced concentration of Hb in the blood.

Polycythemia

Characterized by a higher than normal concentration of Hb in the blood.

P_{50}

In simple anemia and polycythemia, the P_{50} does not change without tissue hypoxia; e.g., a PO_2 of 26 mm Hg will produce 50% saturation of arterial hemoglobin.

Figure VII-3-4 illustrates the effects of an increase and a decrease in hemoglobin concentration. The main change is the plateau or carrying capacity of the blood. Note that the point halfway up each curve, the P_{50}, is still close to 26 mm Hg.

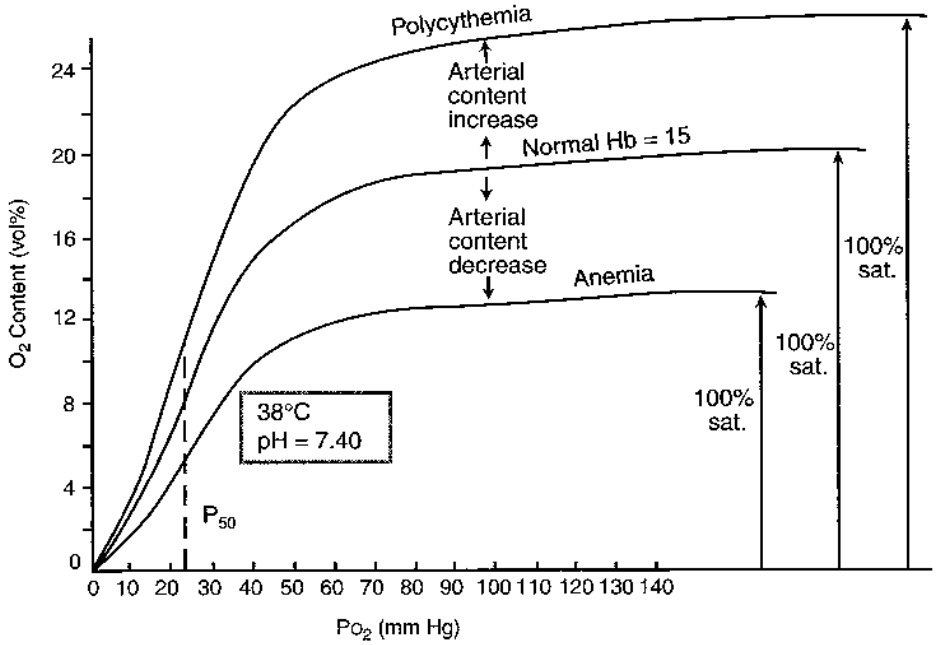


Figure VII-3-4. Effect of Hemoglobin Content on O_2 Content

Effects of Carbon Monoxide

Carbon monoxide (CO) has a greater affinity for Hb than does oxygen (240 times greater). The partial pressure of CO in the blood is close to zero and all the CO molecules are attached to Hb. Figure VII-3-5 shows that with CO the O_2–Hb dissociation curve is shifted to the left and carrying capacity is reduced.

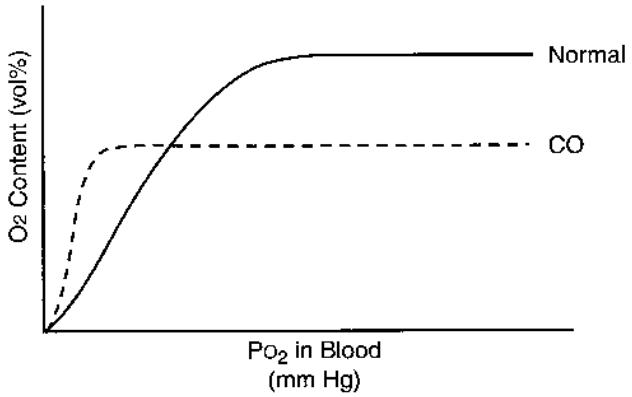


Figure VII-3-5. Carbon Monoxide Poisoning

Table VII-3-1 is a summary of the effects of anemia, polycythemia, and carbon monoxide poisoning.

Table VII-3-1. Systemic Arterial Blood

	PO_2	Hb Concentration	O_2 per g Hb	O_2 Content
Anemia	N	↓	N	↓
Polycythemia	N	↑	N	↑
CO poisoning (acute)	N	N	↓	↓

N = normal; O_2 per g Hb = % saturation.

In anemia, hemoglobin is saturated but arterial oxygen content is depressed because of the reduced concentration of hemoglobin.

In polycythemia, arterial oxygen content is above normal because of an increased hemoglobin concentration.

In CO poisoning, arterial PO_2 is normal, but oxygen saturation of hemoglobin is depressed.

TRANSPORT OF CARBON DIOXIDE

Dissolved Carbon Dioxide

Carbon dioxide is 24 times more soluble in blood than oxygen is. Even though the blood has a PCO_2 of only between 40 and 47 mm Hg, about 5% of the total CO_2 is carried in the dissolved form.

Carbamino Compounds

Carbon dioxide reacts with terminal amine groups of proteins to form carbamino compounds. The protein involved appears to be almost exclusively hemoglobin. About 5% of the total CO_2 is carried as carbamino compounds. The attachment sites that bind CO_2 are different from the sites that bind O_2.

Bicarbonate

About 90% of the CO_2 is carried as plasma bicarbonate.

In order to convert CO_2 into bicarbonate or the reverse, carbonic anhydrase (CA) must be present.

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Figure VII-3-6 illustrates the steps in the conversion of CO_2 into bicarbonate in a systemic capillary.

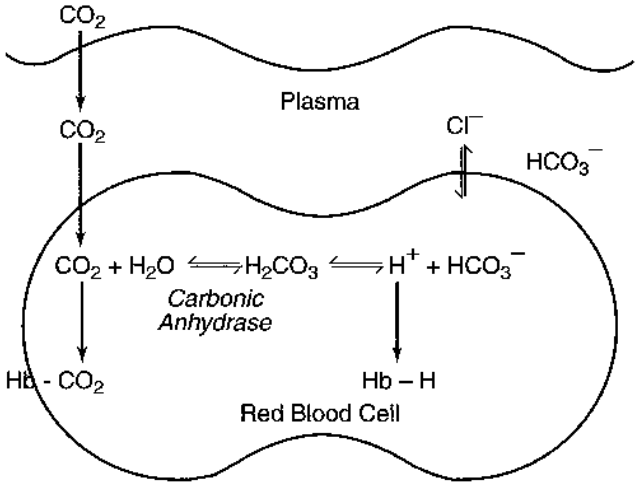


Figure VII-3-6. Formation of Bicarbonate Ion

Plasma contains no carbonic anhydrase; therefore, there can be no significant conversion of CO_2 to HCO_3^- in this compartment.

Because deoxygenated Hb is a better buffer, removing oxygen from hemoglobin facilitates the formation of bicarbonate in the red blood cells (Haldane effect).

To maintain electrical neutrality as HCO_3^- moves into the plasma, Cl^- moves into the red blood cell (chloride shift).

In summary, the bicarbonate is formed in the red blood cell but it is carried in the plasma compartment.

The PCO_2 determines the volume of CO_2 carried in each of the forms listed above. The relationship between the PCO_2 and the total CO_2 content is direct and nearly linear, as shown in Figure VII-3-7.

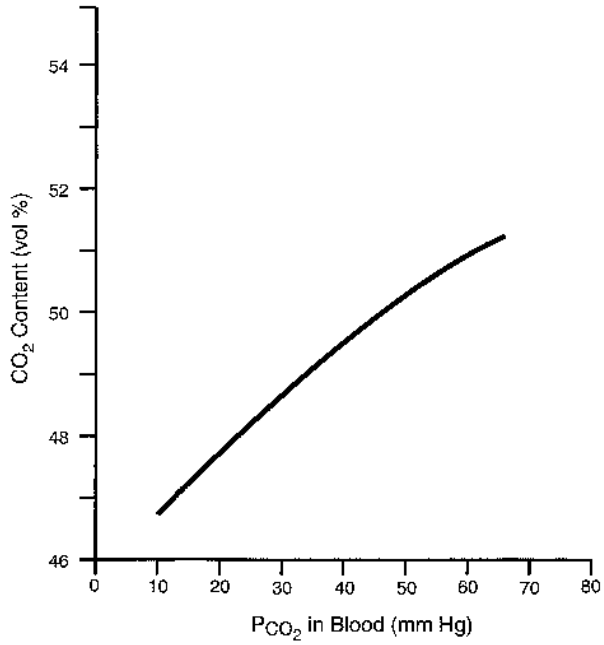


Figure VII-3-7. CO_2 Content in Blood

THE REGULATION OF ALVEOLAR VENTILATION

The level of alveolar ventilation is driven mainly from the input of specific chemoreceptors to the central nervous system. The stronger the stimulation of these receptors, the greater the level of alveolar ventilation. Chemoreceptors monitor the chemical composition of body fluids. In this system, there are receptors that respond to pH, PCO_2, and PO_2. There are two groups of receptors, and they are classified based upon their location.

Central Chemoreceptors

These receptors are located in the central nervous system—more specifically, close to the surface of the medulla.

The receptors directly monitor and are stimulated by cerebrospinal fluid $[H^+]$ and CO_2. The hydration of CO_2 and subsequent dissociation of H_2CO_3 in the CSF generates H^+. CSF H^+ is the stimulus to the central chemoreceptor.

Because the blood–brain barrier is freely permeable to CO_2, the activity of these receptors changes with increased or decreased systemic arterial PCO_2.

These receptors are very sensitive and represent the main drive for ventilation under normal resting conditions at sea level.

Therefore, the main drive for ventilation is CO_2 (H^+) on the central chemoreceptors.

Figure VII-3-8 illustrates the relationship between the central chemoreceptors and the systemic arterial blood.

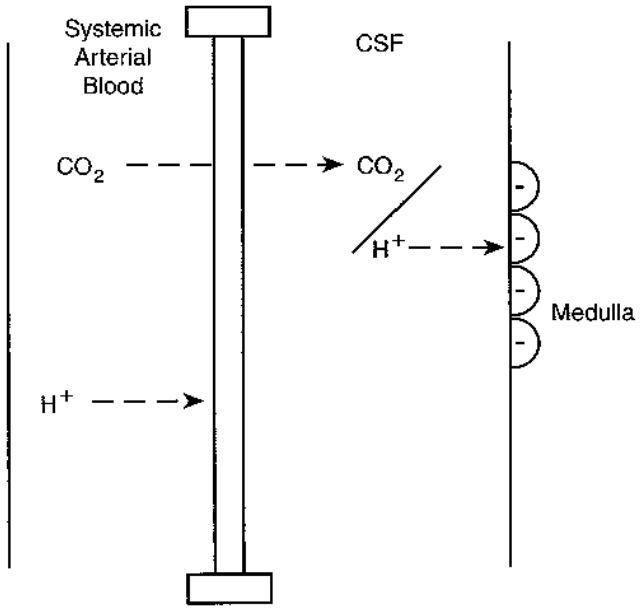


Figure VII-3-8. Central Chemoreceptors

The system does adapt, usually within 12 to 24 hours. The mechanism of adaptation may be the pumping of HCO_3^- into or out of the CSF. There are no central PO_2 receptors.

Also, the central chemoreceptors can be considered very sensitive to any change in CSF H^+ but much less sensitive to a change in systemic arterial H^+. This is due to the fact that H^+ passes slowly across the blood–brain barrier.

Ventilation responds much more to moderate increases of arterial CO_2 (hypercapnia) than it does to relatively large decreases of arterial PO_2.

Peripheral Chemoreceptors

These receptors are found within small bodies at two locations:

Carotid bodies: near carotid sinus, afferents to CNS in glossopharyngeal nerve IX

Aortic bodies: near aortic arch, afferents to CNS in vagus nerve X

The carotid body is the most important peripheral chemoreceptor in humans. Because it receives the most blood per gram of tissue in the body and is so small, it can meet all of its metabolic requirements for O_2 by utilizing the O_2 that is dissolved in the blood. The peripheral chemoreceptors are bathed in arterial blood, which they monitor directly. These bodies have two different receptors:

1. H^+/CO_2 receptors

   These receptors are less sensitive than the central chemoreceptors, but they still contribute to the normal drive for ventilation.

   Therefore, under normal resting conditions at sea level, for all practical purposes, the total drive for ventilation is CO_2, mainly via the central chemoreceptors but with a small contribution via the peripheral chemoreceptors.

2. PO_2 receptors

   The factor monitored by these receptors is PO_2, not oxygen content. Because they respond to PO_2, they are actually monitoring dissolved oxygen and not oxygen on Hb. When systemic arterial PO_2 is close to normal (≅100 mm Hg) or above normal, there is little if any stimulation of these receptors. Thus, they do not contribute to our normal drive for ventilation.

   They are strongly stimulated only by a dramatic decrease in systemic arterial PO_2. Under these conditions, there is an increased drive for ventilation, and alveolar ventilation usually increases. In most situations where the systemic arterial PO_2 is dramatically reduced, the main drive for ventilation is the low PO_2 stimulation of the peripheral chemoreceptors. Sensitivity to hypoxia increases with CO_2 retention.

These receptors do not adapt.

Abnormal Situations

Chronic hypoventilation

Though the $PaCO_2$ is increased, only the peripheral chemoreceptors are driving respiration. Giving supplemental oxygen to these individuals and raising the arterial PO_2 dramatically can raise arterial CO_2.

Anemia

Total O_2 content is decreased, but the PaO_2 is normal. Therefore, there is no ventilatory response to this kind of hypoxia. This also applies to CO poisoning, and in addition, because of the leftward shift in the oxy–Hb dissociation curve, it is life-threatening.

The Central Respiratory Centers

Medullary centers

Site of the inherent rhythm for respiration.

Inspiratory center

Expiratory center

For spontaneous breathing, an intact medulla must be connected to the diaphragm (via the phrenic nerve). Thus a complete C1 or C2 lesion will prevent diaphragmatic breathing but not a complete C6 or lower lesion.

Figure VII-3-9 illustrates the main features involved in the central control of ventilation.

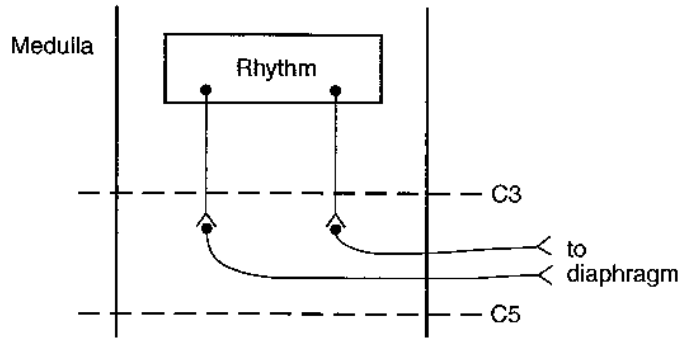


Figure VII-3-9. CNS Respiratory Centers

Abnormal Breathing Patterns

Apneustic breathing: prolonged inspirations alternating with a short period of expiration. This pattern is attributed to the loss of the normal balance between vagal input and the pons-medullary interactions. Lesions in patients with apneustic breathing are usually found in the caudal pons.

Biot's breathing: irregular periods of apnea alternating with periods in which several breaths of identical depth are taken. It is seen in patients with increased intracranial pressure and with certain midbrain lesions.

Cheyne-Stokes breathing: periodic type of breathing which has cycles of gradually increasing depth and frequency followed by a gradual decrease in depth and frequency between periods of apnea. It may result from midbrain lesions but also occurs in infants or during sleep, particularly at high altitude.

UNUSUAL ENVIRONMENTS

High Altitude

At high altitude, atmospheric pressure is reduced from 760 mm Hg of sea level. Because atmospheric pressure is a factor that determines room air and alveolar PO_2, these two values are also reduced. These two values are permanently depressed unless enriched oxygen is inspired.

Therefore, PAO_2 <100 mm Hg, PaO_2 <100 mm Hg, and the low arterial PO_2 will stimulate the peripheral chemoreceptors and increase alveolar ventilation. At high altitude, then, the main drive for ventilation changes from CO_2 on the central chemoreceptors at sea level to a low PO_2 drive of the peripheral chemoreceptors, and hyperventilation ensues.

Table VII-3-2. Acute Changes and Long-Term Adaptations (Acclimatization)

	Acute Changes	Acclimatization
PAO_2 and PaO_2	decreased	remains decreased
$PACO_2$ and $PaCO_2$	decreased	remains decreased
Systemic arterial pH	increased	decreases to normal via renal compensation
Hb concentration	no change	increases (polycythemia)
Hb % sat	decreased	remains decreased
Systemic arterial O_2 content	decreased	increases to normal

At high altitude, hypoxia can develop, resulting in increased circulating levels of erythropoietin. Erythropoietin will increase red blood cell production and eventually cause an adaptive polycythemia.

High-Pressure Environment

In a hyperbaric environment breathing room air (21% O_2 and 79% N_2), the partial pressure of O_2 and N_2 will increase in the alveoli and systemic arterial blood. The pressure of nitrogen will also increase in other body compartments. The adverse effect of a high PO_2 can be oxygen toxicity. The high PN_2 can cause nitrogen narcosis, but, more important, it can lead to the bends (caisson disease).

There are two prerequisites for the bends/caisson disease:

- Breathing high-pressure nitrogen for a prolonged period of time
- Sudden decompression

The sudden decompression causes bubbles of nitrogen (emboli) in the bloodstream and tissues. Treatment is recompression and a slow, gradual decompression.

Chapter Summary

* The only significant form in which oxygen is delivered to systemic tissues is oxygen attached to hemoglobin. However, PO_2 created by dissolved oxygen is a force necessary to keep oxygen bound to hemoglobin.
* Normal hemoglobin in the systemic arterial system will be almost completely saturated with oxygen when the PO_2 is 100 mm Hg. Mixed venous hemoglobin in a resting individual will be about 75% saturated.
* Increased H^+, CO_2, temperature, and 2,3-diphosphoglycerate will shift the Hb–O_2 curve to the right. This assists in the unloading of oxygen to systemic tissues but does not prevent complete loading of oxygen in lung capillaries.
* The normal drive for ventilation is CO_2, mainly on the central chemoreceptors.
* When the systemic arterial PO_2 dramatically decreases, the main drive for ventilation is the low PO_2 on the peripheral chemoreceptors.
* Spontaneous rhythmic breathing requires an intact medulla connected, via the phrenic nerve, to the diaphragm.
* At high altitude, there is a permanent depression in alveolar and systemic arterial PO_2. The low PO_2 stimulates the peripheral chemoreceptors, inducing a hyperventilation and a decrease in alveolar and systemic arterial PCO_2. The loss of CO_2 produces a respiratory alkalosis. To compensate, the kidney loses bicarbonate to return arterial pH close to normal. Acutely, arterial oxygen content is depressed because of reduced hemoglobin saturation. Acclimatization returns oxygen content toward normal because of an increase in hemoglobin concentration.

Four Causes of Hypoxemia

NORMAL STATE

In the normal individual, alveolar ventilation maintains a $PACO_2$ close to 40 mm Hg and a PAO_2 of about 100 mm Hg. Equilibration will occur between the alveolar and pulmonary capillary compartments, and thus pulmonary end capillary blood PCO_2 and PO_2 will equal alveolar. The mismatch between alveolar ventilation and blood flow that is normally present leads to a difference between PO_2 in end capillary and systemic arterial blood (A–a gradient about 5–10 mm Hg).

In the normal lung, the alveolar PO_2 (PAO_2), pulmonary end capillary PO_2, and systemic arterial PO_2 (PaO_2) will have slight differences. This is illustrated in Figure VII-4-1. This is the alveolar–arterial oxygen gradient (A–a gradient). The A–a gradient in a normal subject breathing room air should not exceed 10 mm Hg. Increased A–a gradient indicates lung disease.

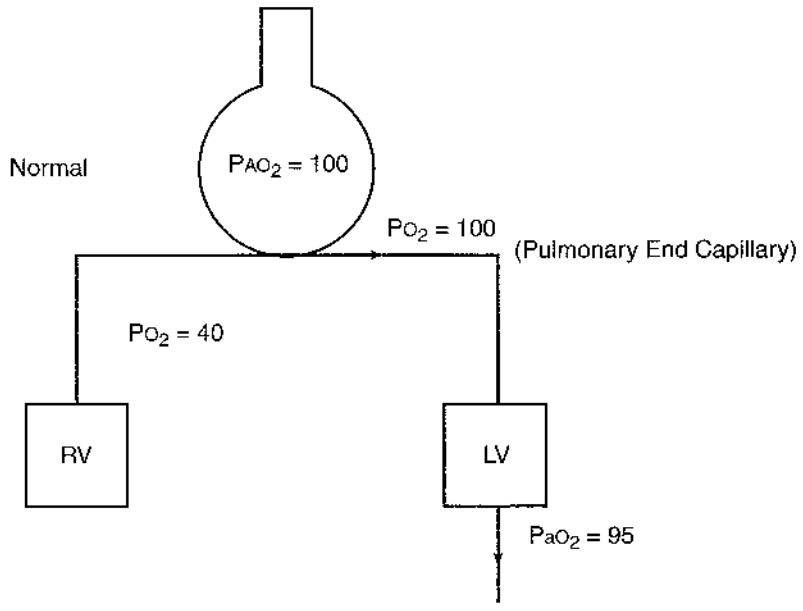


Figure VII-4-1. Normal State

HYPOVENTILATION

Hypoventilation of the entire lung elevates alveolar PCO_2, and the increase in PCO_2 decreases PO_2. For example, if alveolar ventilation decreases by 50%, alveolar PCO_2 becomes 80 mm Hg (an increase of 40 mm Hg). Assuming a respiratory ratio close to 1.0, alveolar PO_2 will decrease by about 40 mm Hg to 60 mm Hg. If no other problem exists, pulmonary end capillary and systemic arterial PO_2 will also decrease by 40 mm Hg. This is illustrated in Figure VII-4-2.

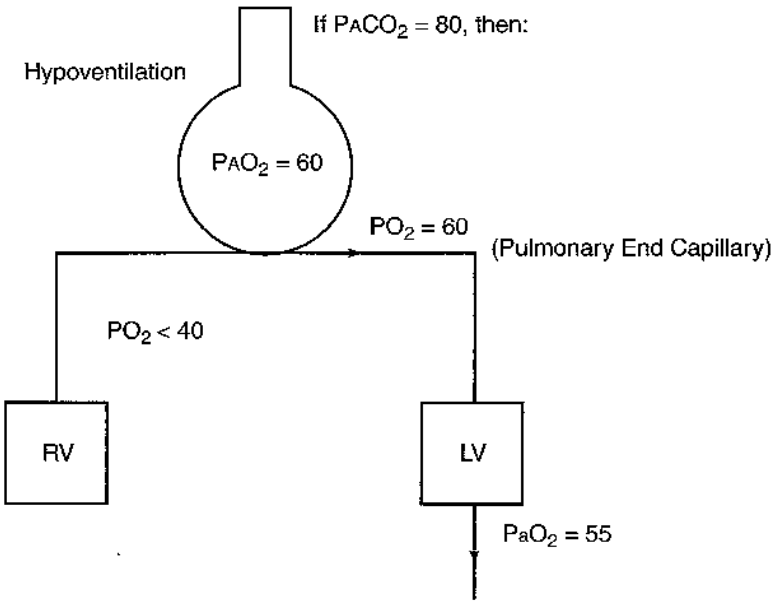


Figure VII-4-2. Hypoventilation

Hypoventilation is characterized as an equal decrease in PO_2 in all three compartments.

As a result, there will not be an increase in the alveolar, systemic arterial PO_2 difference (A–a normal), and end-tidal PO_2 will still be a good index of systemic arterial PO_2.

In patients who are hypoxemic and retaining CO_2, if the PO_2 A–a is normal, one can assume that gas exchange is not defective and that the observed hypoxemia can be corrected entirely by increasing ventilation. This could also be achieved by increasing the inspired oxygen. If PO_2 A–a is elevated, there is a defect in gas transfer.

Also, because arterial PO_2 decreases in hypoxemia, systemic venous and pulmonary arterial PO_2 will also decrease.

In summary

- There is no increase in the A–a oxygen gradient.
- Supplemental oxygen can relieve the hypoxemia.
- End-tidal air still reflects the systemic arterial compartment.
- The problem is not within the lung itself.

DIFFUSION IMPAIRMENT

Diffusion impairment means a structural problem in the lung. This can be produced by a decreased surface area and/or increased thickness of lung membranes. The consequences of diffusion impairment are illustrated in Figure VII-4-3 and summarized following the figure.

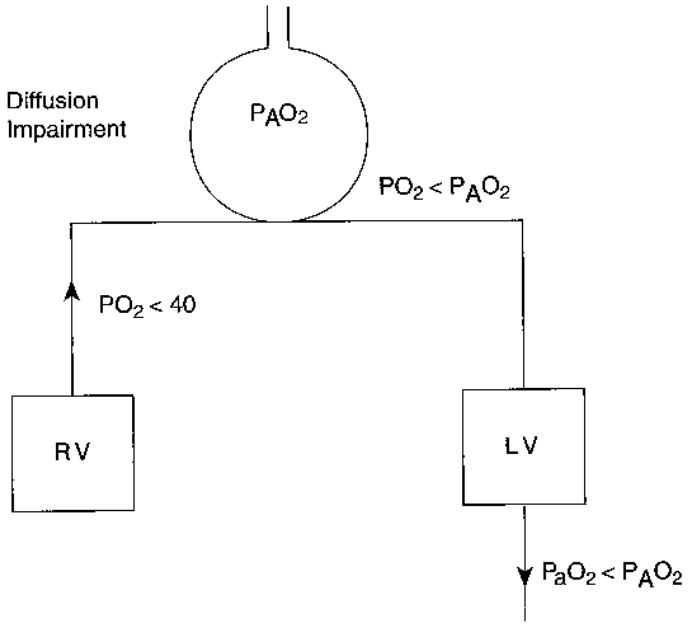


Figure VII-4-3. Diffusion Impairment

In marked diffusion impairment, pulmonary end capillary PO_2 will be less than alveolar PO_2, and a difference will exist between the alveolar and systemic arterial blood (A–a). Thus, end-tidal PO_2 will not be a good index of systemic arterial PO_2. An A–a gradient greater than 10 mm Hg on room air tends to indicate a diffusion problem.

In diffusion impairment, supplemental oxygen will increase the pressure gradient across the alveolar membranes and return arterial PO_2 to normal. Note that although the arterial PO_2 may be restored to normal, or even above normal by supplemental oxygen, there is still an abnormally large A–a gradient.

In summary

- There is an increase in A–a oxygen gradient.
- Supplemental oxygen can relieve the hypoxemia.
- End-tidal air does not reflect the arterial values.
- It is characterized by a decrease in DLCO.

PULMONARY SHUNT

A pulmonary shunt is also known as a right-to-left shunt. By definition, systemic venous blood is delivered to the left side of the heart without exchanging oxygen and carbon dioxide with the alveoli. A good example is blood passing through a region of atelectasis. A right-to-left shunt always leads to hypoxemia.

Figure VII-4-4 illustrates the consequences of a pulmonary shunt. The solid-line regions represent the normal areas of the lung. The dashed line represents the shunted blood, which is passing from the right heart to the left heart without a change in chemical composition.

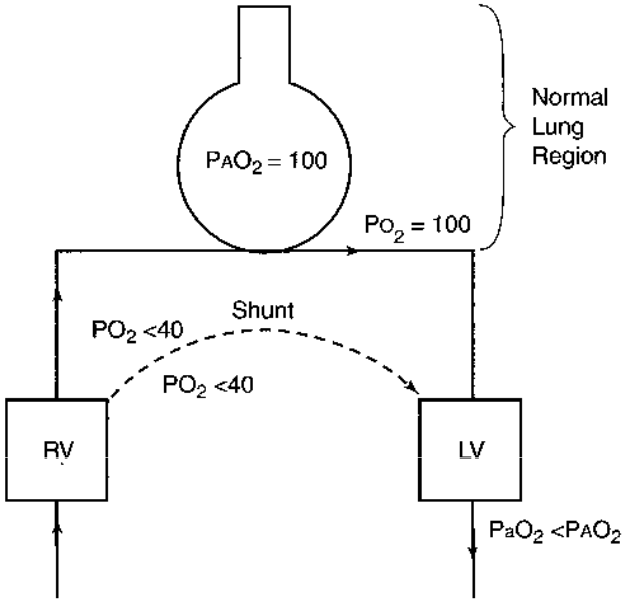


Figure VII-4-4. Pulmonary Shunt

With a pulmonary shunt, systemic arterial PO_2 will be less than alveolar and end-capillary PO_2. A widening of the PO_2 A–a difference will occur, and end-tidal PO_2 will not reflect systemic arterial PO_2.

When a significant pulmonary shunt exists, breathing pure O_2 will elevate systemic arterial PO_2 a small amount, but it will never produce full saturation of the hemoglobin. See Figure VII-4-9 for response of PaO_2 with shunt.

The failure to obtain a significant increase in arterial PO_2 following the administration of supplemental oxygen in hypoxemia is strong evidence of the presence of a pulmonary shunt.

In summary

- Increase in A–a oxygen gradient
- Supplemental oxygen ineffective at returning arterial PO_2 to normal
- End-tidal air does not reflect the arterial values

VENTILATION–PERFUSION DIFFERENCES IN THE LUNG

Regional Differences in Ventilation

At the end of a normal expiration, the mean value for intrapleural pressure is –5 cm H_2O. However, there are regional differences, and the reason for these differences is gravity. In an upright individual, there is a column of fluid and tissue in the chest cavity. Toward the lung apex (against gravity), intrapleural pressure decreases (becomes more negative); more toward the lung base, pressure increases (becomes more positive). These differences are illustrated in Figure VII-4-5.

At the apex, intrapleural pressure is –10 cm H_2O, which represents a low pressure but a large force expanding the alveoli. Therefore, at the beginning of inspiration, alveoli at the apex are large and stiff and contain a large volume of air.

At the base, intrapleural pressure is –2.5 cm H_2O, which represents a higher pressure but a smaller force expanding the alveoli. Therefore, at the beginning of inspiration, alveoli at the base are small and very compliant and contain a small volume of air.

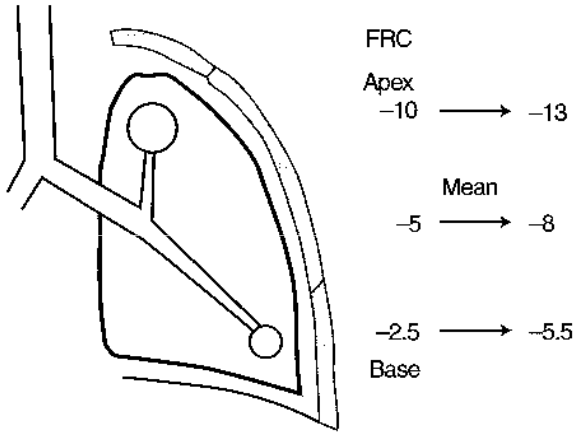


Figure VII-4-5. Upright Posture

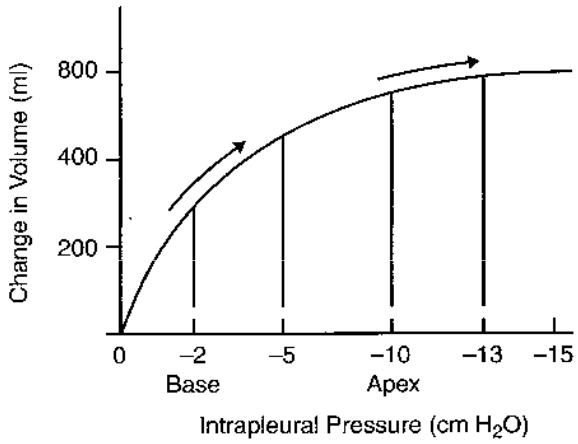


Figure VII-4-6. Regional Ventilation

Inspiration at the apex

Intrapleural pressure decreases from –10 to –13 cm H_2O. But because the alveoli were almost completely inflated (low compliance) before inspiration begins, they change little during inspiration. Thus, very little room air flows into these alveoli. The amount of room air entering an alveolus during inspiration represents alveolar ventilation ($\dot{V}A$). Consequently, under resting conditions, alveoli at the apex are large but receive a low level of alveolar ventilation.

Inspiration at the base

Intrapleural pressure decreases from –2.5 to –5.5 cm H_2O. The base alveoli at the beginning of inspiration are small, but they are on the steep part of the pressure–volume curve (very compliant). Because of this, during inflation there is a large change in size and volume. Consequently, under resting conditions, alveoli at the base are always smaller than those at the apex but receive a high level of alveolar ventilation.

Regional Differences in Blood Flow

Even in a normal individual, there are regional differences in blood flow through the pulmonary circuit. These differences, for the most part, can be attributed to the effect of gravity. In the upright individual, as blood moves against gravity (toward the lung apex), pressure decreases, and as blood moves toward the base of the lung, pressure increases.

Toward the apex

Pulmonary arterial pressure decreases.

Vessels are less distended and thus represent a higher resistance system.

Therefore, lower perfusing pressures and higher resistance mean less blood flow to the apex.

Toward the base

Pulmonary arterial pressure increases.

Vessels are more distended, thus a lower resistance system.

Therefore, no loss in perfusing pressure and a lower resistance pathway mean more blood flow to the base.

Ventilation–Perfusion Relationships

Apex: Least ventilation (mL/min) and blood flow (mL/min)

Base: Greatest ventilation (mL/min) and blood flow (mL/min)

Blood flow and ventilation are greatest at the base and decrease toward the apex. Although the relationship between the two is similar, quantitative differences exist.

In the normal individual, there is an ideal relationship between blood flow and ventilation. The ideal relationship in a normal individual under resting conditions is close to 0.8.

Figure VII-4-7 shows the relative differences in blood flow (Q) and alveolar ventilation ($\dot{V}A$) between the lung base and apex in an upright individual.

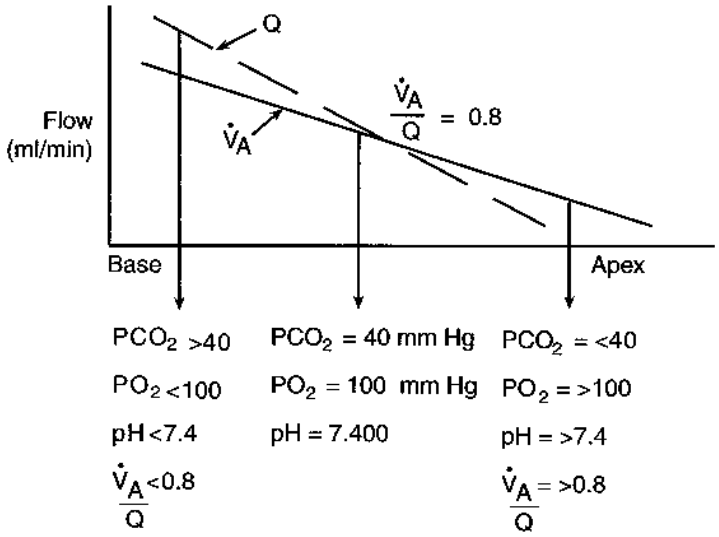


Figure VII-4-7. Ventilation–Perfusion Relationships

Even though the base receives the greatest ventilation, it is not high enough for the very high blood flow. Therefore, the base can be considered an underventilated region.

Even though the apex receives the least ventilation, it is still too high for the very low blood flow. Therefore, the apex can be considered an overventilated region.

In summary

When the ratio is less than 0.8 under resting conditions, the lung unit is underventilated.

When the ratio is greater than 0.8, it is overventilated.

Problem

The following ratios represent two different lung units under resting conditions:

$\dot{V}_A/Q$

A = 0.62

B = 0.73

Both lung units A and B are underventilated, but of the two, B is better ventilated.

Which lung unit had the greatest:

$PACO_2$, end capillary PCO_2? (Answer: A)

PAO_2, end capillary PO_2? (Answer: B)

end capillary pH? (Answer: B)

Hypoxic Vasoconstriction

This is a clinically important phenomenon that is unique to the pulmonary circulation. Whenever there is a decrease in alveolar PO_2, a local vasoconstriction of pulmonary blood vessels is produced. The result is a lowering of blood flow through that lung unit.

Problem

If a person inhales a peanut that lodges in a peripheral airway, what changes would you expect for the following variables in the peanut-occluded unit?

$PACO_2$ (increase)

PAO_2 (decrease)

pulmonary end capillary pH (decrease)

blood flow in that lung unit (decrease)

All answers here are based on the fact that blocking the airway would decrease the $\dot{V}A/Q$ ratio, producing a shunt-like state, as shown in Figure VII-4-8. The blood flow decreases because of hypoxic vasoconstriction. Low $\dot{V}A/Q$ ratios are associated with hypoxic vasoconstriction.

Problem

If a small thrombus lodges in a pulmonary artery, what changes would you expect for the following variables in the thrombus-occluded unit?

$PACO_2$ (decrease)

PAO_2 (increase)

pulmonary end capillary pH (increase)

All answers here are based on the fact that the thrombus would increase the $\dot{V}A/Q$ ratio. This produces lung units that act as dead space, as shown in Figure VII-4-8.

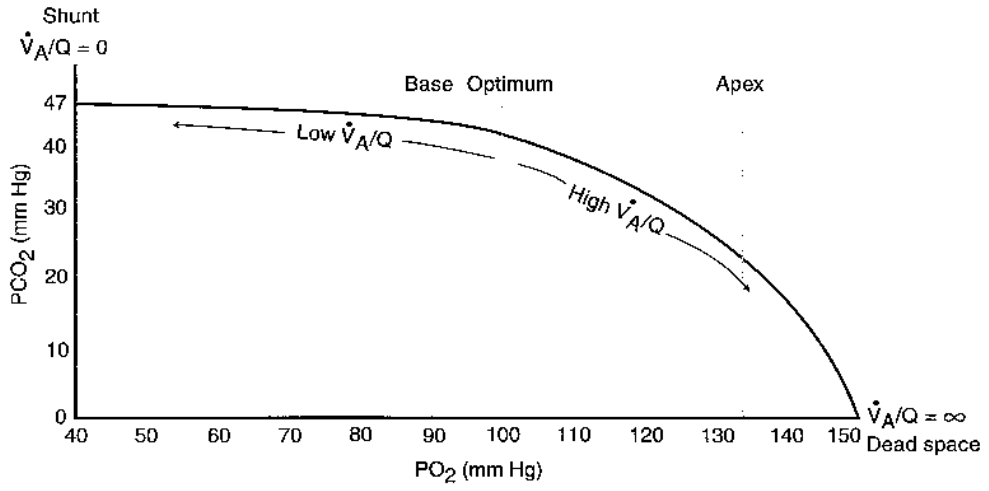


Figure VII-4-8. Shunt and Dead Space

Consequences of $\dot{V}_A/Q$ Mismatches

$\dot{V}_A/Q$ <0.8: If we take the situation to the extreme, where there is blood flow but minimal ventilation, this lung unit would resemble a pulmonary shunt. Thus, as the ratio goes below 0.8, the lung unit begins to act like a shunt. The lower the ratio, the more that lung unit acts like a pure shunt.

$\dot{V}_A/Q$ >0.8: If we take this situation to the extreme, where there is ventilation but minimal blood flow, the lung unit would act as dead space. The greater the ratio, the more that lung unit acts like dead space.

Supplemental oxygen can, in most cases, correct the hypoxemia associated with $\dot{V}_A/Q$ mismatches. An important exception to this is when more than a few percent of the cardiac output perfuses regions of the lung in which there is poor gas exchange, a shunt-like condition. In this case supplemental oxygen has little effect on arterial PO_2. The reason for this is that blood that is shunted has low oxygen content, but blood that has abnormally high $\dot{V}_A/Q$ has high PO_2 with only normal oxygen content (you cannot overload blood with oxygen because of hemoglobin saturation).

A useful estimate of the percentage of the cardiac output that is shunted can be obtained when a patient is breathing 100% oxygen; divide the A–a gradient on pure oxygen by 20. The result is the percentage of shunted blood. For example, if the A–a gradient on pure oxygen is 200 mm Hg, the shunt is about 10% of the cardiac output.

Response to supplemental oxygen with varying percentage of cardiac output that is shunted.

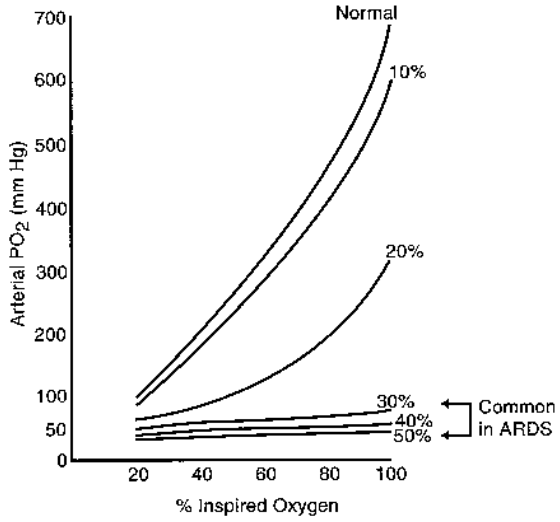


Figure VII-4-9. Response to Supplemental Oxygen

Exercise

In exercise, there is increased ventilation and pulmonary blood flow. The ideal $\dot{V}_A/Q$ is no longer 0.8; it is greater than 0.8. Thus, during exercise, ventilation increases more than cardiac output. Also, the base–apex flows are more uniform.

In summary

- There is an increase in the A–a oxygen gradient.
- Supplemental oxygen can relieve the hypoxemia but is less effective as V/Q decreases to low values.
- End-tidal air does not reflect the systemic arterial values.
- Hypoxemia is often associated with normal or below-normal arterial PCO_2.

SHUNTING OF BLOOD IN THE HEART

The consequences are quite different from a pulmonary shunt because pressures are usually higher on the left side of the heart (atria and ventricles), and thus flow is normally left to right. A major characteristic is that hypoxemia never develops in a left-to-right shunt. The principal example is an atrial or ventricular septal defect.

Figure VII-4-10 illustrates the normal PO_2 values in the left and right compartments. Note from the descriptions that follow where the first increase in PO_2 develops on the right side.

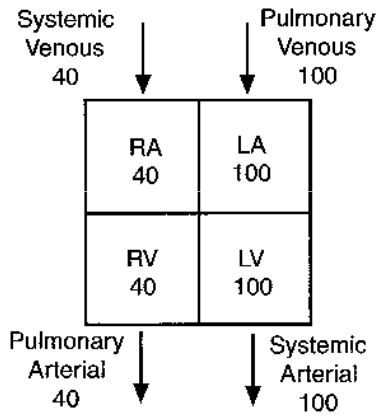


Figure VII-4-10. Left-to-Right Cardiac Shunts

Table VII-4-1. The Consequences of Three Different Left-to-Right Shunts

	Atrial Septal Defect	Ventricular Septal Defect	Patent Ductus (newborn)
Systemic arterial PO_2	no change	no change	no change
Right atrial PO_2	↑	no change	no change
Right ventricular PO_2	↑	↑	no change
Pulmonary arterial PO_2	↑	↑	↑
Pulmonary blood flow	↑	↑	↑
Pulmonary arterial pressure	↑	↑	↑

Atrial septal defect: PO_2 increase first appears in the right atrium.
Ventricular septal defect: PO_2 increase first appears in the right ventricle.
Patent ductus: PO_2 increase appears in pulmonary artery.

If pressures on the right side exceed those on the left, the situation is equivalent to a pulmonary shunt. If, for example, pressure in the right atrium exceeds left atrial pressure, a septal defect will produce a right-to-left shunt, and the oxygen content of the blood in the left heart will decrease.

Chapter Summary

* Hypoventilation is associated with equal decreases in the PO_2 of the alveolar, pulmonary end capillary, and systemic arterial compartments. There is no widening of the A–a gradient, and an increase in alveolar ventilation will return arterial PO_2 to normal. This can also be achieved with supplemental oxygen.
* Diffusion impairment is a structural problem of the lung. When it is severe, blood leaving a pulmonary capillary will not have equilibrated with the alveolar air. There is a widening of the A–a gradient, and supplemental oxygen will return arterial PO_2 toward normal.
* A pulmonary (right-to-left) shunt will produce a widening of the A–a gradient and is the only cause of hypoxemia that will not respond significantly to supplemental oxygen.
* The ideal $\dot{V}A/Q$ ratio at rest is close to 0.8. A ratio greater than 0.8 is an overventilated lung unit (dead-space component), and a ratio less than 0.8 is an underventilated lung unit (pulmonary shunt component).
* A low $\dot{V}A/Q$ ratio or any other decrease in alveolar PO_2 will initiate a vasoconstriction of the pulmonary vasculature.
* A left-to-right shunt can lead to pulmonary hypertension but will not produce hypoxemia.

SECTION VIII

Renal Physiology

Renal Structure and Glomerular Filtration

INTRODUCTION TO THE RENAL SYSTEM

Overall Functions of the Kidney

- Secretes hormones into the circulation; renin (enzyme), 1,25 dihydroxy-Vit D, erythropoietin.
- Excretes waste products: urea, uric acid, creatinine
- Water and electrolyte balance
- Acid/base balance

Functional Organization of the Kidney

Figure VIII-1-1 illustrates the cortical versus the medullary organization of the kidney. Nephrons with glomeruli in the outer cortex have short loops of Henle (cortical nephrons). Those with glomeruli in the inner cortex have long loops of Henle, which penetrate the medullary region (juxtamedullary nephrons).

- 7/8 of all nephrons are cortical nephrons
- 1/8 of all nephrons are juxtamedullary nephrons

Nephron structures in the medulla consist of the long loops of Henle and the terminal regions of the collecting ducts. All other structures, including the first section of the collecting ducts, are in the cortex.

In the cortex, the proximal and distal tubules, as well as the initial segment of the collecting duct, are surrounded by a capillary network, and the interstitium is close to an isotonic environment (300 mOsm). The medullary region instead has capillary loops organized similar to the loops of Henle. The slow flow through these capillary loops preserves the osmolar gradient of the interstitium. However, this slow flow also keeps the PO2 of the medulla lower than that in the cortex. Even though the metabolic rate of the medulla is lower than in the cortex, it is more susceptible to ischemic damage.

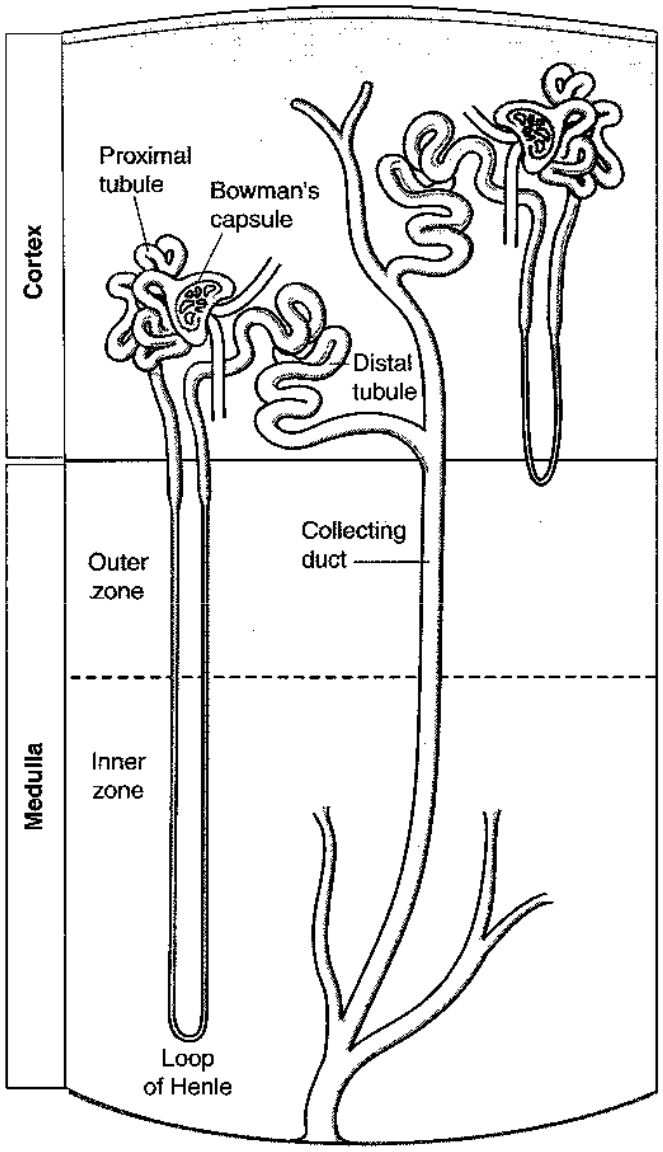


Figure VIII-1-1. Nephron Structures

Autoregulation of Renal Blood Flow and GFR

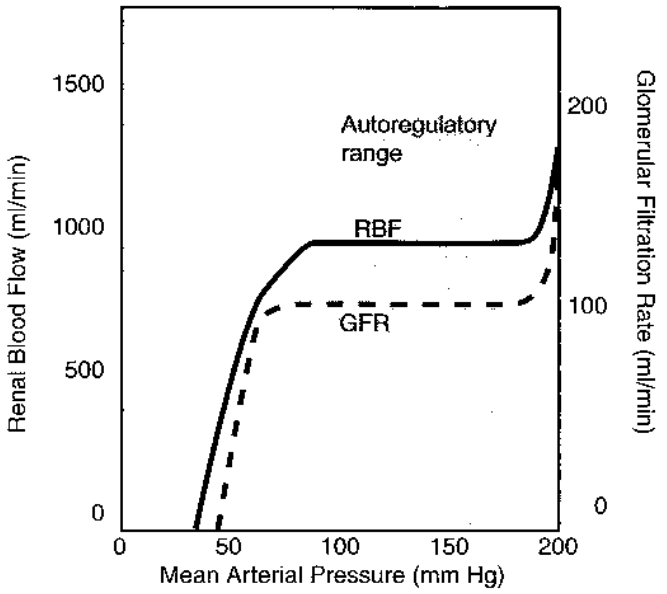


Figure VIII-1-2. Autoregulation and the Renal Function Curve

The autoregulatory range of the kidney is from about 90 to 180 mmHg primarily due to changes in the resistance of the afferent arterioles. Two mechanisms are involved:

- Myogenic responses: This is related to the intrinsic property of smooth muscle to contract when stretched. This concept was presented in Section V, Peripheral Circulation.
- Tubuloglomerular feedback: Delivery of NaCl or chloride ions to the macula densa located at the end of the loop of Henle or beginning of the distal tubule sends a signal that affects the resistance of the afferent arteriole and thus renal blood flow and GFR. A decreased delivery of chloride to the macula densa dilates the arteriole, and an increased delivery of chloride constricts the arteriole. The mediator of this effect is not clear but could be adenosine.

NEPHRON HEMODYNAMICS

Series Hemodynamics

- The individual nephrons that make up both kidneys are connected in parallel. However, the flow through a single nephron represents two arterioles and two capillary beds connected in series.
- The following represents some of the basic consequences of a series hemodynamic system. This information and additional details were presented in Section V, Peripheral Circulation.

Figure VIII-1-3 represents a model with three resistors connected in series.

Flow must be equal at all points in any series system. If flow changes, it changes equally at all points in the system.

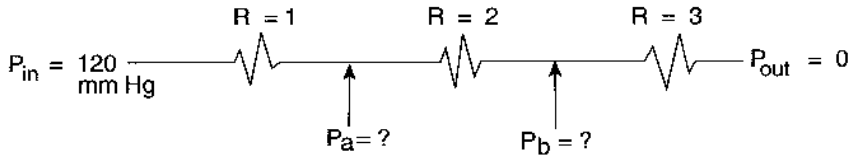


Figure VIII-1-3. Series Circuits

If Pin and Pout are kept constant, the following will occur if the central resistance increases:

- Flow through R1, R2, and R3 will decrease equally.
- Pb pressure downstream decreases.
- Pa pressure upstream increases.

If Pin and Pout are kept constant, the following will occur if the central resistance decreases:

- Flow through R1, R2, and R3 will increase equally.
- Pb pressure downstream increases.
- Pa pressure upstream decreases.

Hemodynamics of a single nephron

Figure VIII-1-4 represents the hemodynamics of a single nephron. Connected in series are the high-pressure filtering capillaries of the glomerulus and the low-pressure reabsorbing peritubular capillaries.

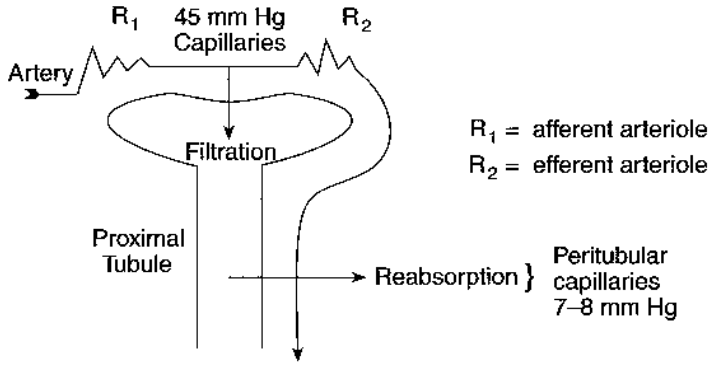


Figure VIII-1-4. Glomerular Hemodynamics

Independent response of the afferent and efferent arterioles

Table VIII-1-1 illustrates the expected consequences of independent isolated constrictions or dilations of the afferent and efferent arterioles.

Table VIII-1-1. Consequences of Independent Isolated Constrictions or Dilations of the Afferent and Efferent Arterioles

	Glomerular Cap Pressure	Peritubular Cap Pressure	Nephron Plasma Flow
Constrict efferent	↑	↓	↓
Dilate efferent	↓	↑	↑
Constrict afferent	↓	↓	↓
Dilate afferent	↑	↑	↑

GLOMERULAR FILTRATION

GFR is the rate at which fluid is filtered into Bowman's capsule. The units of filtration are a volume filtered per unit time, e.g., mL/min or liters/day. In a young healthy male it is about 120 mL/min or about 180 L/day.

If one kidney is removed (1/2 of the functioning nephrons lost), GFR decreases only about 25% because the other nephrons compensate.

The same factors that affected filtration previously discussed for peripheral circulation apply here. The only difference is that fluid is filtering into Bowman's space instead of the interstitium.

The Four Factors Determining Net Filtration Pressure

Figure VIII-1-5 illustrates the role of the four factors that determine net filtration pressure.

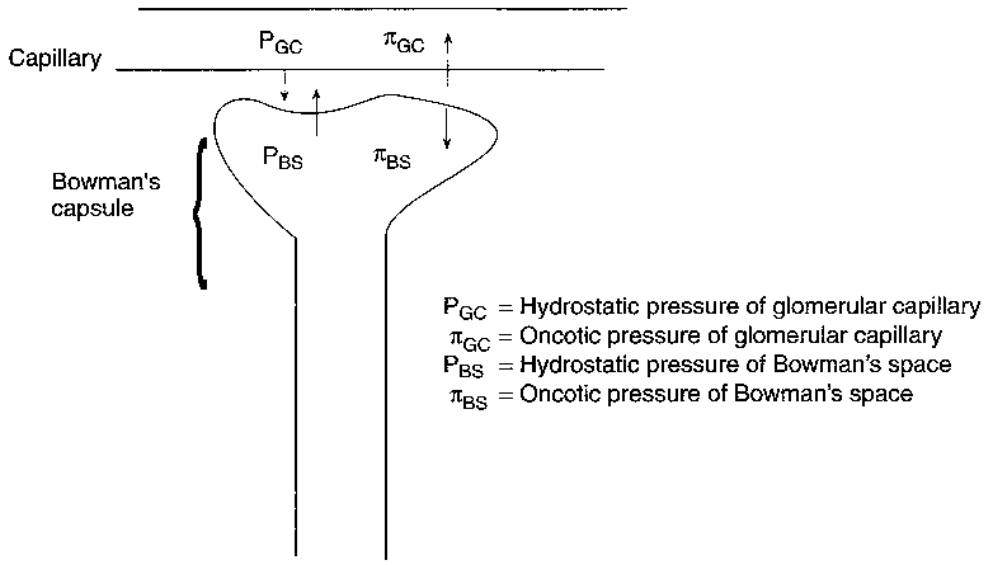


Figure VIII-1-5. Determinants of Filtration

Hydrostatic pressure of the glomerular capillaries

PGC: The hydrostatic pressure of the glomerular capillaries is the only force that promotes filtration. Under normal conditions, this is the main factor that determines GFR.

Oncotic pressure of the plasma

πGC: The oncotic pressure of the plasma varies with the concentration of plasma proteins. Because fluid is filtered but not protein, oncotic pressure, which opposes filtration, will increase from the beginning to the end of the glomerular capillaries (see Figure VIII-1-6). The increased concentration of protein will be carried into the peritubular capillaries and will promote a greater net force of reabsorption.

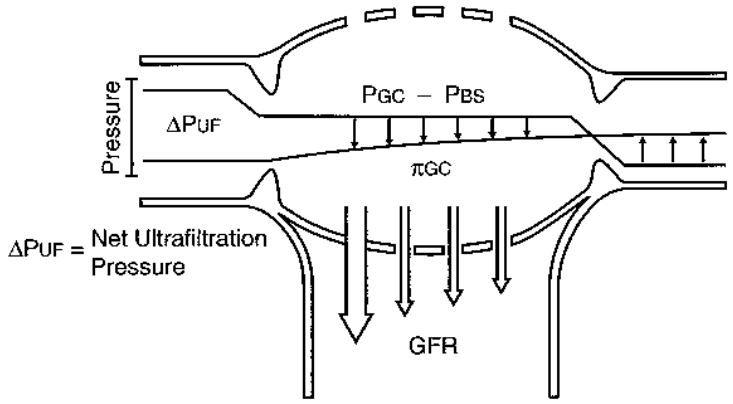


Figure VIII-1-6. Glomerular Filtration

Hydrostatic pressure in Bowman's space

PBS: The hydrostatic pressure in Bowman's capsule opposes filtration. Normally, it is low and fairly constant and does not affect the rate of filtration. However, it will increase and reduce filtration whenever there is an obstruction downstream, such as a blocked ureter or urethra (postrenal failure).

Protein or oncotic pressure in Bowman's space

πBS: This represents the protein or oncotic pressure in Bowman's space. Very little if any protein is present, and for all practical purposes this factor can be considered zero.

Normal Values

PBS = 8 mm Hg PGC = 45 mm Hg

πBS = 0 mm Hg πGC = 24 mm Hg

Net filtration pressure = PGC – πGC – PBS = 45 – 24 – 8 = 13 mm Hg

The Filtering Membrane

The membrane of the glomerulus consists of three main structures:

- Capillary endothelial wall with fenestrations that have a magnitude greater than proteins. In addition the wall is covered with negatively charged compounds.
- A glomerular basement membrane made up of a matrix of extracellular negatively charged proteins and other compounds.
- An epithelial cell layer of podocytes next to Bowman's space. The podocytes have foot processes bridged by filtration slit diaphragms.

Around the capillaries is the mesangium containing mesangial cells, which are similar to monocytes. They can contract and affect GFR and renal blood flow.

The capillary wall with its fenestrated endothelium, the basement membrane with hydrated spaces, and the interdigitating foot processes of the podocytes combined with an overall large surface area, creates a high hydraulic conductivity (permeable to water and dissolved solutes) but restricts the passage of large proteins because of negative charge of the membrane system.

In addition to the net hydraulic force, GFR depends on both the permeability and the surface area of the filtering membrane. The decrease in GFR in most diseased states is due to a reduction in the membrane surface area. This would also include a decrease in the number of functioning nephrons.

Materials Filtered

The following are **easily** or **freely filtered**:

- Major electrolytes: sodium, chloride, potassium, bicarbonate
- Metabolic waste products: Urea Creatinine
- Metabolites: glucose, amino acids, organic acids (ketone bodies)
- Nonnatural substances: inulin, PAH (p-aminohippuric acid)
- Lower-weight proteins and peptides: insulin, myoglobin

The following are **not freely filtered**:

- Albumin and other plasma proteins
- Lipid-soluble substances transported in the plasma attached to proteins such as lipid-soluble bilirubin, T4 (thyroxine), other lipid-soluble hormones

Fluid Entering Bowman's Capsule

- The fluid entering Bowman's space is an ultrafiltrate of plasma; that is, the filtrate has the same concentration of dissolved substances as plasma, except proteins.
- The osmolarity of the filtrate is 300 mOsm/L. The criteria for effective osmolarity are the same as those previously stated for extracellular fluid (Section I).
- If a substance is freely filtered by the kidney, the ratio of the filtrate concentration to plasma concentration TF/P = 1.0. This means the concentrations in Bowman's space and the plasma will be the same.

Distribution of Flow in the Normal Kidney

The following formula for the filtration fraction (FF) and the normal values given should be memorized.

FF = fraction of the material that enters the kidney that is filtered
normally 0.20 or 20% for a freely filtered substance

$$FF = \frac{GFR}{RPF} \qquad GFR = 120 \text{ mL/min} \qquad RPF \text{ (renal plasma flow)} = 600 \text{ mL/min}$$

$$= \frac{120 \text{ mL/min}}{600 \text{ mL/min}} = 0.20 \text{ or } 20\%$$

Determinants of GFR

- Except for an unusual situation when plasma protein concentration changes dramatically or renal obstruction develops, the main factor determining GFR is glomerular capillary pressure.
- An increase in capillary pressure increases GFR, and a decrease in capillary pressure decreases GFR.

Factors Affecting Filtration Fraction (FF)

- In many circumstances, the main factor affecting FF is renal plasma flow. The longer the fluid remains in the glomerular capillaries, the greater the percentage of the fluid that tends to be filtered.
- Therefore, as flow decreases, FF will always have a tendency to increase.
- Based on the preceding discussion, the following should be expected for afferent versus efferent constriction:

	Afferent Constriction	Efferent Constriction
Glomerular filtration pressure	↓	↑
GFR	↓	↑
RPF	↓	↓
FF		↑

Effects of Sympathetic Nervous System

Stimulation of the sympathetic neurons to the kidney causes vasoconstriction of the arterioles. As a consequence:

- ↓ GFR
- ↑ FF
- ↑ Forces promoting reabsorption in the peritubular capillaries because of a lower capillary hydrostatic pressure and an increase in plasma oncotic pressure (proteins are more concentrated)

Overall less fluid is filtered and a greater percentage of that fluid will be reabsorbed in the proximal tubule. There is no parasympathetic innervation of the kidney.

Effects of Angiotensin II (AII)

Because angiotensin constricts the efferent more than the afferent arterioles, it tends to preserve glomerular capillary pressure as renal resistance increases and plasma flow decreases. Thus, GFR may show only a minimal decrease under these conditions.

Filtered Load

Filtered load is the rate at which a substance is filtered into Bowman's space. Units are an amount per unit time, e.g., mg/min.

$$\text{Filtered load} = \text{GFR} \times P_x$$

GFR = glomerular filtration rate

units = volume/time, e.g., mL/min, L/day

Px = free (not bound to protein) concentration of the substance in the plasma.

units = amount/volume, e.g., mg/mL

Question: Given the following information, calculate the filtered load of the preceding substances.

GFR = 120 mL/min

Plasma glucose = 100 mg/100 mL

Inulin = 2 mg/mL

Plasma bicarbonate = 24 mEq/L

Answer: glucose: 120 mg/min, inulin: 240 mg/min, bicarbonate: 2.88 mEq/min

CLINICAL ESTIMATION OF GFR AND THE CONCEPT OF CLEARANCE

- Estimates of GFR are used clinically as an index of renal function and to assess the severity and the course of renal disease.
- A fall in GFR means the disease is progressing, whereas an increase in GFR suggests a recovery.
- In many cases a fall in GFR may be the first and only clinical sign of renal dysfunction.
- Estimations of GFR rely on the concept of clearance.

Clearance

Clearance refers to a theoretical volume of plasma from which a substance is removed over a period of time. For example:

If the concentration of substance x is 4 molecules per liter and the excretion of x is 4 molecules per minute, the volume of plasma cleared of x is 1 L per minute.

If the excretion of x decreases to 2 molecules per minute, the volume cleared of x is only 0.5 L per minute.

If the concentration of x decreases to 2 molecules per liter of plasma and the excretion is maintained at 2 molecules per minute, the cleared volume is back to 1 L per minute. These numbers are summarized in Table VIII-1-2 below.

Table VIII-1-2. Example Calculations of Clearance Values

Plasma Concentration (molecules/L)	Excretion Rate (molecules/minute)	Volume Cleared (L/minute)
4	4	1.0
4	2	0.5
2	2	1.0

Thus, the two factors that determine clearance are the plasma concentration of the substance and its excretion rate.

$$\text{Clearance of x} = \frac{\text{Excretion rate of x}}{\text{Px}} = \frac{\text{Ux} \times \text{V}}{\text{Px}}$$

Ux = urine concentration of x
V = urine flow rate
Px = plasma concentration of x

The plasma concentration of the substance and its urine concentration must be in the same units, which will then cancel.

Urine flow (V) is a volume per unit time, and the units of V will become the units of clearance. Clearance is a volume of plasma cleared of a substance per unit time, mL/min or L/day.

Question: Using the following information, calculate the clearance of x, y, and z.

V = 2 mL/min	
Ux = 2 mg/mL	Px = 2 mg/mL
Uy = 0 mg/mL	Py = 13.6 mg/mL
Uz = 0.5 mg/mL	Pz = 1 mg/mL

Answer: x = 2 mL/min, y = 0, and z = 1 mL/min

Clearance as an Estimate of GFR

Substances having the following characteristics can be used to estimate GFR.

- Stable plasma concentration that is easily measured
- Freely filtered into Bowman's space
- Not reabsorbed, secreted, synthetized, or metabolized by the kidney

Ideal substances would include inulin, sucrose and mannitol. Even though the clearance of inulin is considered the gold standard for the measurement of GFR, it is not used clinically. Instead clinical estimates of GFR rely on creatinine.

Creatinine is released from skeletal muscle at a constant rate proportional to muscle mass. Muscle mass decreases with age but GFR also normally decreases with age.

Creatinine is freely filtered and not reabsorbed by the kidney, although a very small amount is secreted into the proximal tubule.

Creatinine production = creatinine excretion = filtered load of creatinine = Pcr × GFR

Thus, if creatinine production remains constant, a decrease in GFR would be reflected by an increase in plasma creatinine concentration, and an increase in GFR would be reflected by a decrease in plasma creatinine.

Plasma creatinine, however, is not a very sensitive measure of reduced GFR. It will only reveal large changes in GFR.

As shown in Figure VIII-1-7, a significant reduction of GFR can occur with only modest elevation of plasma or serum creatinine concentration.

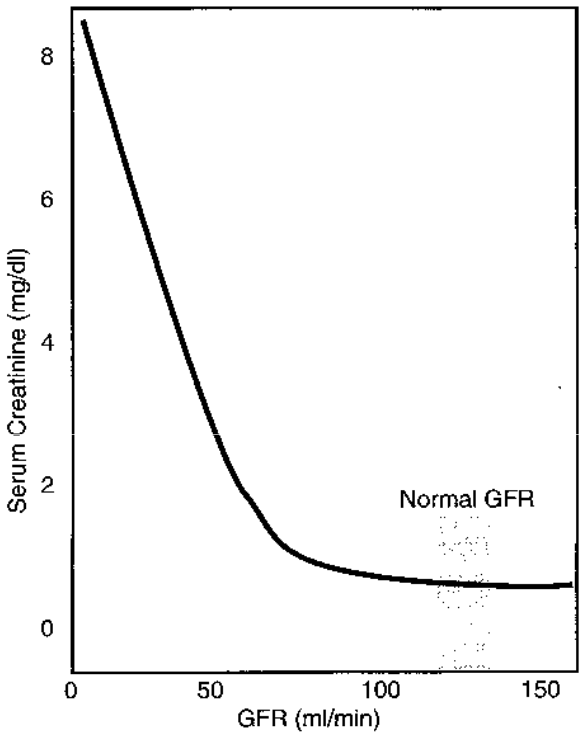


Figure VIII-1-7. Serum Creatinine as Index of GFR

The only practical numerical estimate is the calculated clearance of creatinine. The following is all that is needed:

- Plasma creatinine concentration
- Timed collection of urine and the urine's concentration of creatinine

CLASSIC PRESENTATIONS OF GLOMERULAR DISEASE

Nephrotic Syndrome

A young man comes to his family physician because of recently developed pitting edema on the lower extremities. Blood pressure is normal. Laboratory results include the following:

Blood chemistry
Creatinine = 0.89 mg/dL
BUN = 13 mg/dL
Albumin = 1.6 g/dL

Calculated urine excretion of protein = 7.4 g/day
Urine sediment = occasional hyaline casts, red cells rare, oval fat bodies

This individual displays the classic proteinuria (> 3.5 g/day) of nephrotic syndrome. Some patients are asymptomatic but this individual displays the more severe consequences, i.e., the hypoalbuminemia and edema due to fluid retention and urinary losses of protein.

Nephrotic syndrome reflects a noninflammatory injury to the glomerular membrane system. The damage is usually to the epithelial podocytes or the basement membrane. Immune complexes deposited in this region are less exposed to the circulatory system and fail to create an inflammatory response. Creatinine is usually close to normal, however, there is a decreased surface area for filtration and some decrease in GFR. There also tends to be a high blood cholesterol.

An example would be membranous nephropathy, which usually represents a relatively pure nephrotic syndrome. It is associated with immune complexes deposited along the subepithelial aspect of the basement membrane. The nephrotic pattern in diabetic nephropathy is not immune related. Rather, the hypertension, hyperfiltration, and elevated glucose levels are believed to be the causative agents. There are changes in the mesangial matrix, capillary endothelium, and the basement membrane.

Nephritic Syndrome

A young man comes to his family physician because he noticed the appearance of a dark maroon urine. His blood pressure is 148/107 mm Hg. Laboratory results reveal the following:

Blood chemistry
Creatinine = 2.6 mg/dL
BUN = 36 mg/dL
Albumin = 4.1 g/dL

Urine analysis shows a small amount of protein but many red cells.

Although greater amounts of protein may appear in the urine, the classic pattern is an active urine sediment containing red blood cells, white blood cells, and cellular and granular casts. Typically there is injury to the endothelium or the basement membrane that results in an active inflammatory response. The significant fall in GFR is due to the decrease in surface area available for filtration because of closure of capillary lumens by the inflammatory response. Sodium retention can lead to hypertension.

An example of a nephritic pattern is Alport's syndrome, a progressive glomerulonephritis in which the basement membrane becomes irregular in thickness. It is caused by a defect in the collagen that makes up a major component of the basement membrane. As a result of the inflammation of the capillary endothelium, the membrane system fails to act as an effective filtration barrier to blood cells and protein.

Chapter Summary

* Autoregulatory mechanisms maintain a fairly constant renal blood flow and GFR when blood pressure remains between 90 and 180 mm Hg.
* Individual nephrons are organized in parallel, but the vascular system of each nephron structure (the afferent arteriole, glomerular capillaries, efferent arteriole, and peritubular capillaries) are connected in series.
* The major factor determining GFR is glomerular capillary hydrostatic pressure. The only other important factor in a normal kidney system is the colloid osmotic pressure of the plasma proteins. The glomerular membrane system is permeable to all substances dissolved in plasma except proteins and provides a large surface area for filtration. A loss of surface area can be compensated for by an increase in glomerular capillary pressure.
* FF is mainly determined by renal plasma flow. A decrease in flow tends to increase FF.
* Filtered load is the rate at which a substance is filtered into Bowman's space. For a freely filtered substance it is determined by its plasma concentration and GFR.
* Estimates of GFR are used as clinical indices of renal function. The clearance of inulin is the gold standard but because of the ease of measurement, the plasma concentration of creatinine and the calculated clearance of creatinine are the clinical standards.
* Nephrotic and nephritic syndromes are two classic patterns of glomerular disease. Nephrotic syndrome characteristically is a noninflammatory injury to the glomerular epithelium or basement membrane, resulting in a large proteinuria but only minimal changes in GFR. Nephritic syndrome is an inflammatory response to the glomerular injury, resulting in significantly decreasing GFR and blood cells appearing in the urine.

Solute Transport: Reabsorption and Secretion

GENERAL PRINCIPLES OF SOLUTE TRANSPORT

Transport proteins in the cell membranes of the nephron mediate the reabsorption and secretion of solutes and water transport in the kidneys. Acquired defects in transport proteins are the cause of many kidney diseases. In addition the transport proteins are important drug targets.

Transport Mechanisms

Simple diffusion: as discussed in Section VII, Respiration, net movement represents molecules or ions moving down their electrochemical gradient.

Facilitated diffusion: (facilitated transport) molecule or ion moving across a membrane down its electrochemical gradient attached to a specific membrane-bound protein

Active transport: a protein-mediated transport that uses ATP as a source of energy to move a molecule or ion against its electrochemical gradient

DYNAMICS OF PROTEIN-MEDIATED TRANSPORT

Uniport: transporter moves a single molecule or ion as in the uptake of glucose into skeletal muscle or adipose tissue. A type of facilitative transport

Symport: (cotransport) a coupled protein transport of 2 or more solutes in the same direction as in Na-glucose, Na-amino acid transporters.

Antiport: (countertransport) a coupled protein transport of 2 or more solutes in the opposite direction

Generally protein carriers transport substances that cannot readily diffuse across a membrane. There are no transporters for gases and most lipid-soluble substances because these substances readily move across membranes by simple diffusion.

Characteristics Common to All Protein-Mediated Transport

Rate of transport: A substance is transported more rapidly than it would be by diffusion, because the membrane is not usually permeable to any substance for which there is a transport protein.

Saturation kinetics: As the concentration of the substance initially increases on one side of the membrane, the transport rate will increase. Once the transporters become saturated, transport rate is maximal (TM = transport maximum). TM is the transport rate when the carriers are saturated. It is directly proportional to the number of functioning transporters.

Chemical specificity: To be transported, the substance must have a certain chemical structure. Generally, only the natural isomer will be transported. (e.g., D-glucose but not L-glucose).

Competition for carrier: Substances of similar chemical structure may compete for the same transporter. For example, glucose and galactose will generally compete for the same transport protein.

Primary and Secondary Transport

In primary active transport, ATP is consumed directly by the transporting protein, (e.g., the Na/K-ATPase pump, or the calcium pump (calcium-dependent ATPase) of the sarcoplasmic reticulum).

Secondary active transport depends indirectly on ATP as a source of energy, as in the cotransport of Na-glucose in the proximal tubule. This process depends on ATP utilized by the Na/K-ATPase pump.

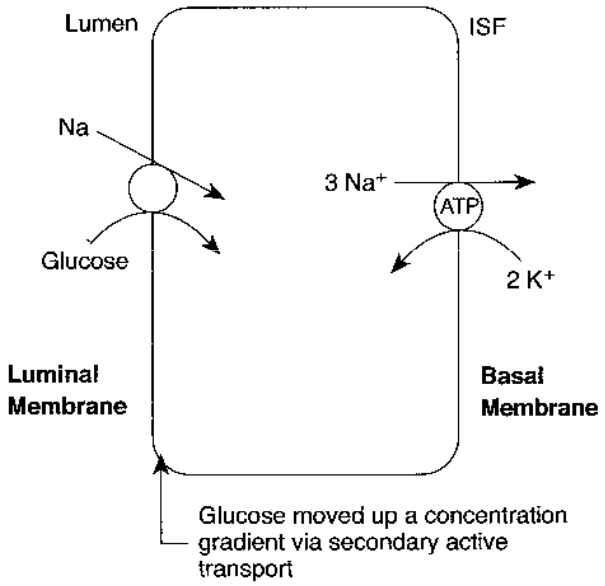


Figure VIII-2-1. Renal Tubule or Small Intestine

Figure VIII-2-1 represents a renal proximal tubular cell. In this figure, the Na/K-ATPase pump maintains a low intracellular sodium concentration, which creates a large gradient across the cell membrane. It is this sodium gradient across the luminal membrane that drives secondary active transport of glucose.

In summary, the secondary active transport of glucose:

- depends upon luminal sodium
- is stimulated by luminal sodium (via increased sodium gradient)
- is linked to the uptake of sodium
- depends upon rate of metabolic ATP production

Another example of secondary active transport is the counter transport of Na- H also in the proximal tubule. As with glucose transport this process depends on the Na/K-ATPase pump. The pumping of H+ out of the tubule cell facilitates further conversion of CO2 to bicarbonate. The bicarbonate then moves via facilitated transport from the cell to the interstitium driven by the high intracellular bicarbonate concentration. In fact, a generalization is that all of the transport which occurs in the proximal tubule is powered by the Na/K-ATPase pump.

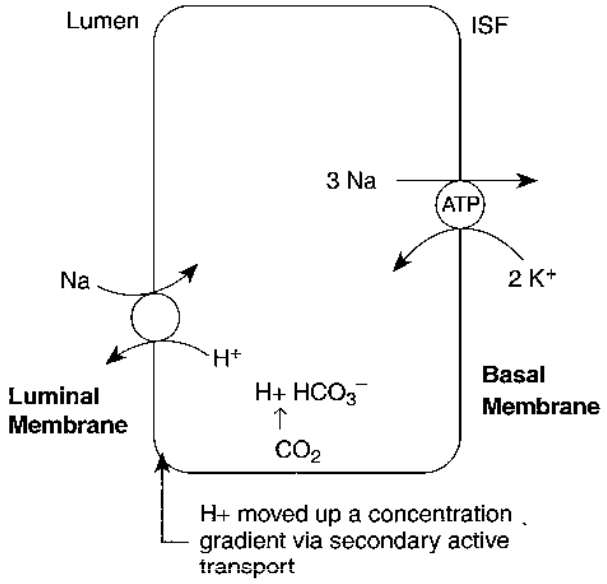


Figure VIII-2-2. Proximal Tubule

ENDOCYTOSIS

Endocytosis is the movement of macromolecules from outside the cell to the inside of the cell by the active invagination of the plasma membrane. The small amount of protein that is normally filtered across the glomerular membrane is reabsorbed by this process. It is active and thus is dependent on ATP.

TUBULAR REABSORPTION

There are two basic types of active reabsorption based on system dynamics: TM and gradient–time system. The latter is now simply referred to as the proximal tubular reabsorption of sodium as it is the only example.

Transport Maximum (TM) Systems

For example, proximal tubular reabsorption of glucose.

General characteristics

- Carriers are easily saturated.
- Carriers have a high affinity for the substrate.
- There is low back leak.

Back leak refers to the back diffusion of the substance into the tubule after it is reabsorbed into the interstitium. Minimal back leak of glucose occurs because the proximal tubule is not permeable to glucose.

Summary Statement

The entire filtered load is reabsorbed until the carriers are saturated; then the excess is excreted.

Dynamics of Glucose Filtration and Reabsorption

Figure VIII-2-3 graphically represents the dynamics of glucose filtration, reabsorption, and excretion.

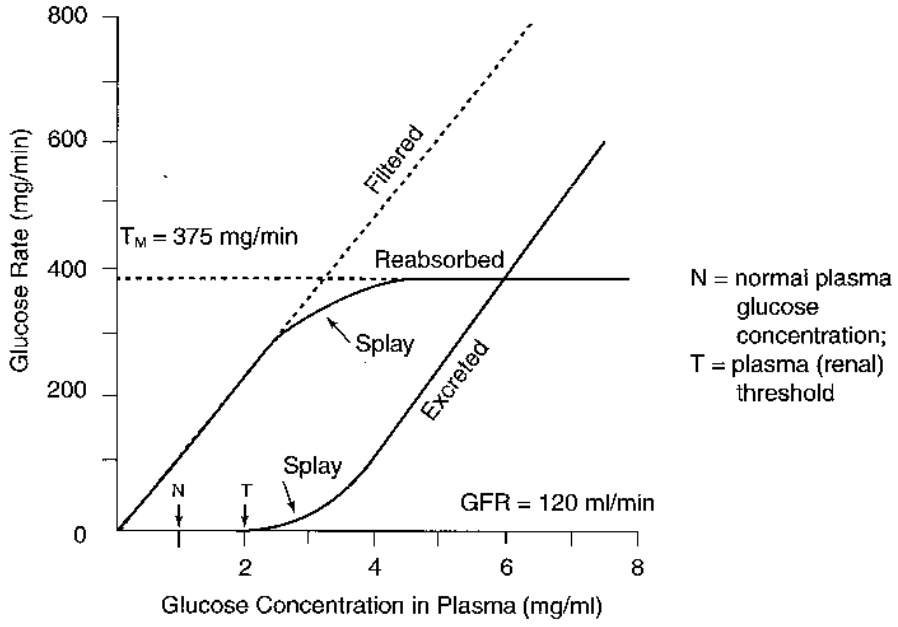


Figure VIII-2-3. Transport Maximum Reabsorption of Glucose

- At low plasma levels, the filtration rate and the reabsorption rate of glucose are equal, thus glucose does not appear in the urine.
- T_M is the maximal reabsorption rate of glucose, i.e., it is the rate when all the carriers are saturated. T_M can be used as an index of the number of functioning carriers.

- The rounding of the reabsorption curve into the plateau is called splay. Splay occurs because some nephrons reach T_M before others. Thus, T_M for the entire kidney is not reached until after the region of splay.
- Plasma (or renal) threshold is the plasma glucose concentration at which glucose first appears in the urine. This occurs at the beginning of splay.

Substances Reabsorbed

Almost all natural organic and some inorganic substances that are reabsorbed by the nephron are reabsorbed by a T_M system. These substances include glucose, amino acids, small peptides and proteins, ketone bodies, calcium, and phosphate. An exception with respect to natural organic substances is urea. Urea is freely filtered and partially reabsorbed, mainly by passive mechanisms. Urea as it passes through the nephron tends to follow the water but not proportionately. More water is reabsorbed than urea, which creates a net excretion for urea.

Proximal Reabsorption of Sodium (Gradient–Time System)

General characteristics

- Carriers appear to be never saturated.
- Carriers have a low affinity for the substrate.
- There is high back leak.

High back leak means that some of the sodium that is actively reabsorbed back diffuses into the proximal tubule. The proximal tubule has leaky tight junctions to sodium and also to a few other substances, such as potassium, chloride, and water.

Summary statement

Approximately a constant percentage of the filtered sodium is reabsorbed in the proximal tubule. Under normal conditions it is close to 66%, which means about two-thirds of the filtered sodium is reabsorbed in the proximal tubule.

This means that if GFR and the filtered load of sodium increases, reabsorption in the proximal tubule also increases. This prevents a dramatic increase in the sodium load delivered distal to the proximal tubule. These segments have a limited capacity to reabsorb sodium. This phenomenon is referred to as glomerular-tubular balance.

Also, the active reabsorption of sodium by the proximal tubule is the main metabolic process going on in the kidney. Thus, oxygen consumption of the kidney is directly proportional to sodium reabsorption and GFR.

TUBULAR SECRETION

Transport Maximum System

p-aminohippuric acid (PAH) secretion

PAH secretion from the peritubular capillaries into the proximal tubule is an example of a transport maximum system. As a T_M system, it has the general characteristics discussed for the reabsorption of glucose except for the direction of transport.

Figure VIII-2-4 illustrates the renal handling of PAH at low plasma concentrations.

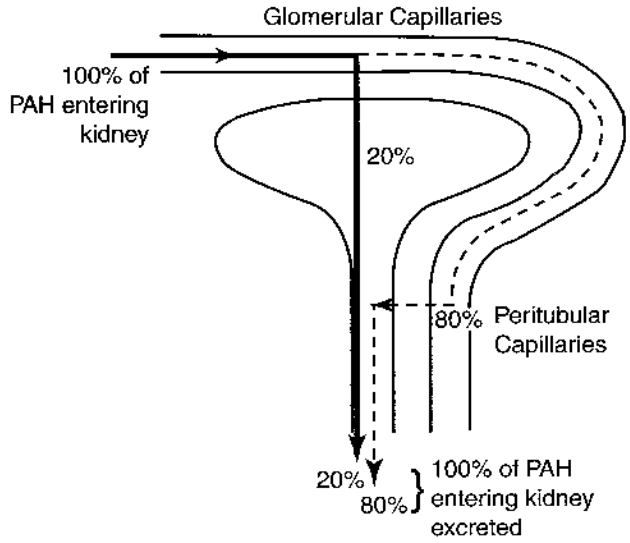


Figure VIII-2-4. Secretion of PAH

Normal values:

Renal plasma flow = 600 mL/min

GFR = 120 mL/min

FF = .20

PAH is freely filtered but no PAH can be reabsorbed. Therefore, all of the PAH filtered in the 120 mL/min is excreted. Thus, the entire volume filtered was completely cleared of PAH. This would occur regardless of the plasma concentration of PAH.

Regardless of the plasma concentration of PAH, the kidney will always clear the volume filtered (GFR).

With the renal plasma flow of 600 mL/min, 480 mL/min (80%) is delivered to the peritubular capillaries.

From the peritubular capillaries, there is a secretory pathway for plasma organic anions, which secretes PAH into the proximal tubule. Since PAH cannot be reabsorbed, all secreted PAH will be excreted. Many non-natural organic anions including antibiotics like penicillin all compete for the same transport system.

The T_M for PAH equals 80 mg/min. Neglecting splay, then:

- If plasma concentration = 0.167 mg/mL, then the load delivered to the peritubular capillaries would be (.167 mg/mL x 480 mL/min) 80 mg/min or T_M.
- If the plasma concentration was ≤ .167 mg/mL, the entire 480 mL/min would be cleared of PAH and the renal venous concentration of PAH would be zero.
- If the plasma concentration was ≥ .167 mg/mL, the entire 480 mL/min would not be cleared of PAH and PAH would appear in the renal venous plasma.
- If the plasma concentration of PAH was 80 mg/mL, then of the 480 mL/min delivered to the peritubular capillaries only 1 mL/min would be cleared of PAH.

- At low plasma concentrations, the clearance of PAH is renal plasma flow (120 via filtration plus 480 via secretion).
- At high plasma concentrations, the clearance is GFR (120 via filtration plus insignificant volume via secretion).

PAH clearance at low plasma concentrations is referred to as effective renal plasma flow (ERPF) because some plasma perfuses the renal capsule. This flow (about 10%) is not cleared of PAH. Thus, PAH clearance is only 90% of the true renal plasma flow.

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{1 - \text{HCT}}$$

If renal plasma flow is 600 mL/min and the Hct is 50%, renal blood flow is 1200 mL/min

Substances secreted in the proximal tubule

PAH is transported by a fairly nonspecific organic anion secretion system. Many compounds will compete for the carriers. In addition to PAH, some of those compounds include:

- Penicillin
- Furosemide
- Acetazolamide
- Salicylate

Because the organic anions all compete for the same carriers, elevation of the plasma level of one ion inhibits the secretion and clearance of the others.

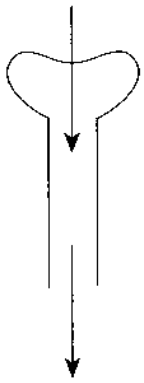
There is a similar transport secretory system for many organic cations. A slightly different transport mechanism is involved but, again, the system is fairly nonspecific. Drugs using this pathway would include:

- Atropine
- Morphine
- Procainamide
- Cimetidine
- Amiloride

It is important to realize that, because of competition for the carrier proteins, the concurrent administration of organic cations can increase the plasma concentration of both drugs to much higher levels than when the drugs are given alone.

NET EFFECTS OF REABSORPTION AND SECRETION

Figure VIII-2-5 illustrates that net transport sometimes referred to as mass balance is determined simply by comparing the filtered load with the excretion rate of a substance. Both variables are expressed as an amount of substance per unit time, and the units must be the same for meaningful comparisons, e.g., mg/min.



Filtered Load = GFR × P_x
amount/time volume/time amount/volume
mg/min ml/min mg/ml

Excretion = U_x × V
amount/time amount/volume volume/time
mg/min mg/ml ml/min

U_x = urine concentration of substance
V = urine flow rate

Figure VIII-2-5. Relationship of Filtered Load and Excretion

No Net Tubular Modification

- Filtered load = excretion rate
- The amount filtered and amount excreted per unit time are always the same, e.g., inulin, mannitol.

Net Reabsorption

- Filtered load > excretion
- Excretion is always less than filtered load, e.g., glucose, sodium, urea.
- If the substance is completely reabsorbed, the rate of filtration and the rate of reabsorption are equal.
- If the substance is partially reabsorbed, excretion is less than filtration.
- Reabsorption = filtration – excretion

Net Secretion

- Filtered load < excretion
- Excretion is always greater than filtered load, e.g., PAH, creatinine.
- Creatinine is freely filtered, and a very small amount is secreted.
- Secretion = excretion – filtered load

The following formula is sometimes used to calculate net transport. The sign of the calculated number will indicate the three basic categories:

0 = no net transport
+ = net reabsorption
– = net secretion

net transport rate = filtered load – excretion rate
= (GFR × Px) – (Ux × V)

Question: Given the following information, calculate the reabsorption rate for glucose.

GFR = 120 mL/min
Plasma glucose = 300 mg/100 mL
Urine flow = 2 mL/min
Urine glucose = 10 mg/mL

Answer: 340 mg/min

The illustrations in Figure VIII-2-6 represent the net transport of specific types of substances for a normal individual on a typical Western diet (contains red meat). The dashed lines represent the route followed by the particular substance. Quantitative aspects are not shown. For example, in B, 20% of the substance entering the kidney is filtered and excreted, and the remaining 80% passes through the kidneys and back into the general circulation without processing. (Note: The illustrations in Figure VIII-2-6 are meant to show overall net transport only.)

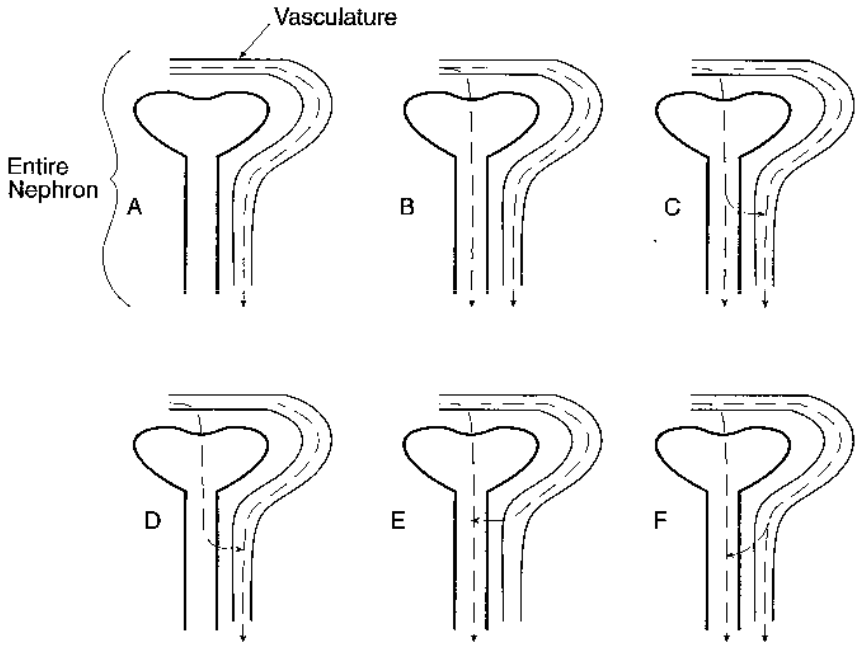


Figure VIII-2-6. Graphical Representation of Transport

Chapter Summary

* Simple diffusion and facilitated transport are both passive processes (not energy-dependent) driven by concentration gradients.
* The rate of protein-mediated transport will increase with increased substrate delivery until the carriers are saturated. The maximum rate of transport (carrier saturation) is called TM, and this rate is directly proportional to the number of functioning carriers present in the system.
* Secondary active transport is driven by the sodium gradient across the cell membrane, which is maintained by the Na/K–ATPase pump.
* Endocytosis and exocytosis represent active uptake and extrusion of macromolecules via vesicular transport.
* The active reabsorption of glucose in the proximal exhibits TM dynamics. Everything filtered is reabsorbed until the carriers in some nephrons are saturated. The plasma level at this point is called plasma (or renal) threshold, and glucose will begin to appear in the urine. This is also at the beginning of the region of splay. All transporters in all nephrons become saturated once the plateau is reached, which is after the region of splay. At this point, the glucose reabsorption rate is maximal (T_M). T_M is an index of the number of functioning nephrons.
* The active secretion of PAH in the proximal tubule exhibits TM dynamics. At plasma levels below carrier saturation, 20% of the PAH entering the kidney is filtered, and 80% is secreted. All the PAH is excreted, and no PAH appears in the renal venous plasma (excluding plasma flow through the capsule). PAH appears in the renal venous plasma once the carriers in a few nephrons become saturated (beginning of splay).
* If a substance is freely filtered and exhibits:
  - no net transport, filtered load = excretion rate
  - net reabsorption, filtered load is > excretion rate
  - net secretion, filtered load is < excretion rate

General Patterns of Clearance

The following list represents type substances ranked from the smallest volume cleared by the kidney to the largest volume cleared. From your understanding of clearance and how the kidney handles a particular substance, its relative clearance and changes in clearance can be easily determined.

Glucose: The normal clearance of glucose is zero. This is simply due to the fact that no glucose appears in the urine. As soon as renal threshold is reached, glucose appears in the urine; it has a positive clearance.

Sodium: Sodium always appears in the urine, thus sodium always has a positive clearance. To clear a volume of plasma the substance in that volume must be excreted. Reabsorption of a filtered substance decreases the volume cleared. The higher the percentage of the filtered load reabsorbed, the smaller the volume cleared. Since almost the entire filtered load of sodium is reabsorbed its clearance is just above zero. Aldosterone by increasing the reabsorption of sodium decreases its clearance. Atrial natruritic factor increases the clearance of sodium by causing a sodium diuresis.

Urea: Urea is freely filtered but partially reabsorbed. Because some urea will always be present in the urine, you will always clear a portion of the 120 mL/min filtered into Bowman's space. Since urea tends to follow the water and excretion is flow dependent, a diuresis increases urea clearance and an antidiuresis decreases urea clearance. Note that with a small volume of concentrated urine, the concentration of urea is relatively high, but the excretion will be less than in a diuresis which has a much lower concentration of urea. It is the large volume in the diuresis that increases the urea excretion and clearance.

Inulin: Inulin is freely filtered and there is no transport. As mentioned previously its clearance always equals GFR regardless of its plasma concentration.

Creatinine: If a substance is freely filtered and what is filtered is always excreted, the substance will always have a clearance at least as great as GFR. It will be greater than GFR if, in addition some is secreted and that secreted amount is also excreted. The more that is secreted in a steady state the higher the clearance climbs above GFR. Since with creatinine everything filtered is excreted plus a small amount secreted and excreted, it has a clearance slightly greater than GFR.

PAH: The greatest clearance via the kidney is renal plasma flow this is the clearance of PAH at low plasma concentrations, 120 mL/min by filtration and 480 mL/min by secretion. As such there would be no PAH in the renal venous blood. Following saturation not all of the 480 mL/min delivered to the peritubular capillaries would be cleared, and clearance would decrease below renal plasma flow.

CLEARANCE CURVES FOR SOME CHARACTERISTIC SUBSTANCES

Figure VIII-3-1 plots clearance versus increasing plasma concentration for four substances. A description of each curve follows the figure. Since the clearance of many substances does not correlate with their plasma concentration, a curve on the graph below for those substances is not possible.

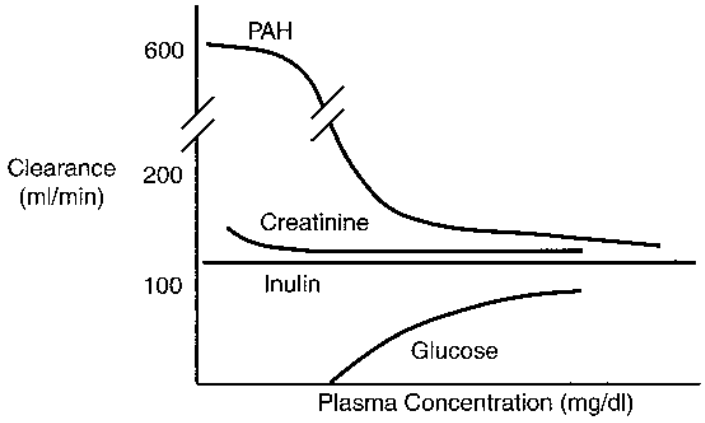


Figure VIII-3-1. Clearance Curves

Inulin

Inulin produces a line parallel to the *x* axis, and the intersection point on the *y* axis represents GFR. In other words inulin's clearance is independent of its plasma concentration. If GFR increases, the line shifts upward; likewise, if GFR decreases, the line shifts down. It is always parallel to the *x* axis, and the point of intersection with the *y* axis is always GFR.

Glucose

At low plasma levels, the clearance of glucose is zero. As the plasma level rises, glucose will appear in the urine once the carriers are saturated in some nephrons. The plasma level at which glucose first appears in the urine is called the plasma (or renal) threshold, and at this point glucose will have a positive clearance. As the plasma level rises further, the clearance will increase and approach that of inulin. The clearance will never equal inulin because some glucose will always be reabsorbed. If the reabsorption of glucose was completely inhibited, the clearance of glucose would equal inulin and GFR.

Creatinine

The clearance of creatinine will always be slightly greater than inulin and GFR because creatinine is filtered and a small amount exhibits net secretion in the proximal tubule. However, creatinine clearance parallels inulin clearance and is independent of production rate (excretion rises as plasma concentration increases). Since it is endogenously produced, it is not necessary to infuse it to get a clearance measurement, as has to be done to measure inulin clearance. Therefore, the clearance of creatinine is the preferred clinical method for determining GFR.

PAH

At low plasma concentrations, the clearance equals renal plasma flow. As the plasma concentration rises, the carriers in some nephrons will reach saturation. At this point, some PAH will appear in the renal venous plasma, and the clearance will be less than renal plasma flow. As the plasma level rises further, the clearance approaches but never equals GFR because some PAH is always secreted. If the secretion of PAH was completely suppressed, the clearance would exactly equal GFR.

FREE WATER CLEARANCE

Free water clearance is the best measure of the balance between solute and water excretion. Its use is to determine whether the kidneys are responding appropriately to maintain normal plasma osmolarity. Free water clearance is how much solute-free water is being excreted; it is as if urine consisted of plasma (with solutes) plus or minus pure water.

- If urine osmolarity was 300 mOsm/L (isotonic urine), free water clearance would be zero.
- If plasma osmolarity is too low, urine osmolarity should be lower still (positive free water clearance) in order to compensate.
- Positive-free water clearance tends to cause increased plasma osmolarity; negative free water clearance causes reduced plasma osmolarity.
- C_{H2O} (+) = hypotonic urine is formed (osmolarity <300 mOsm/L)
- C_{H2O} (–) = hypertonic urine is formed (osmolarity >300 mOsm/L)

$$C_{H_2O} = V - \frac{U_{osm} V}{P_{osm}}$$

V = urine flow rate
U_{osm} = urine osmolarity
P_{osm} = plasma osmolarity

$$V = C_{H_2O} + C_{osm}$$

Sample Calculation

$\dot{V}$ = 3.0 mL/min

U_{osm} = 800 mOsm/L

P_{osm} = 400 mOsm/L

C_{H_2O} = –3 mL/min

Conclusion: The kidneys are conserving water; this is appropriate compensation for the excessive plasma osmolarity in this patient.

Chapter Summary

* Substances that do not appear in the urine have a clearance of zero.
* Substances freely filtered and partially reabsorbed have a clearance less than the GFR.
* Substances freely filtered with no net transport like inulin have a clearance equal to GFR.
* Substances freely filtered and with net secretion like creatinine have a clearance greater than the GFR. Because only a very small amount of creatinine is secreted, it always has a clearance slightly greater than GFR.
* Substances freely filtered and the remainder entering the kidney completely secreted will have a clearance equal to renal plasma flow.
* Free water clearance is a theoretical volume excreted without solute. It is used to evaluate if the renal balance of solute and water excretion is appropriate.

Regional Transport

THE PROXIMAL TUBULE

The fluid entering the proximal tubule is the isotonic ultrafiltrate (300 mOsm/L). The concentration of a freely filtered substance in this fluid will equal its plasma concentration. Figure VIII-4-1 illustrates the main cellular transport processes of the proximal tubular cells. A summary follows.

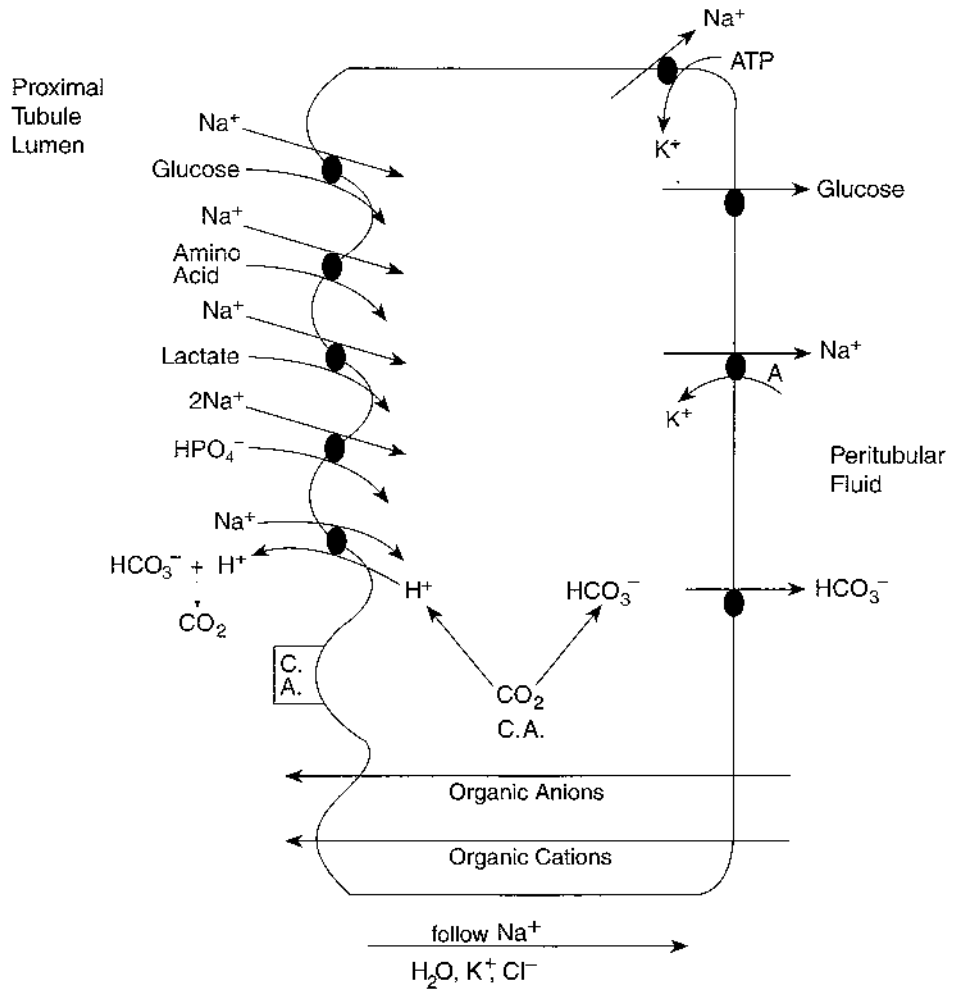


Figure VIII-4-1. Transport in Proximal Tubule

Proximal Tubule Changes

Water and electrolytes

Approximately 2/3 of the filtered sodium is reabsorbed in the proximal tubule by primary and secondary active transport.

About two-thirds of the filtered H_2O, K+, and almost two-thirds of the filtered Cl– follow the sodium (leaky system to these substances), and the osmolarity at the end of the proximal tubule remains close to 300 mOsm/L (isosmotic reabsorption). The chloride concentration rises slightly through the proximal tubule because of the large percentage of bicarbonate reabsorbed here.

Therefore, at the end of the proximal tubule, osmolarity and the concentrations of Na+ and K+ have not changed significantly from plasma, but only a third of the amount originally filtered remains.

Metabolites

Normally, all carbohydrates, proteins, peptides, amino acids, and ketone bodies are reabsorbed here via secondary active transport (requires luminal sodium, linked to sodium reabsorption).

Therefore, the concentration of the above should be zero in the tubular fluid leaving the proximal tubule (clearance is zero).

Bicarbonate

About 80–90% of the filtered bicarbonate is reabsorbed indirectly here. Because the process simply recovers the amount filtered, there is no net gain or loss of bicarbonate by the body.

The small amount of bicarbonate that leaves the proximal tubule is normally reabsorbed in subsequent segments.

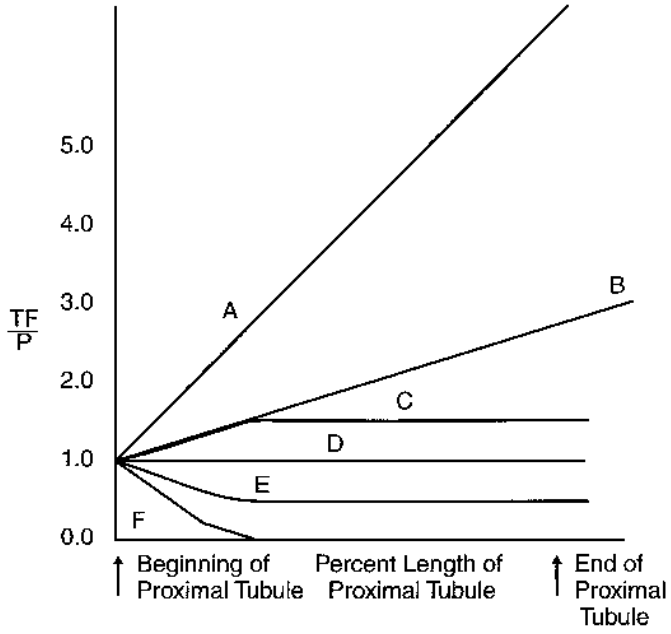
Secretion

The proximal tubule is where many organic anions and cations are secreted and cleared from the circulation including PAH, penicillin, atropine, and morphine.

Energy requirements

Notice that all of the active processes illustrated in Figure VIII-4-1 are powered by the Na/K- ATPase primary active pump. This pump is located in the proximal tubule basal and basolateral borders and is directly or indirectly responsible for most of the water and electrolyte reabsorption in the nephron. It thus represents the most energy-demanding process of the nephron. The nephron also has a H-ATPase that contributes to the active H+ secretion.

Figure VIII-4-2 depicts the ratio of the concentration of the substance in the proximal tubular fluid (TF) to the concentration in the plasma (P).



A = PAH
B = Inulin
C = Substance reabsorbed is somewhat less rapidly than water, e.g., chloride
D = Major electrolytes such as sodium, potassium
E = Substance reabsorbed somewhat more rapidly than water
F = Substance completely reabsorbed in the proximal tubule, e.g., glucose

Figure VIII-4-2. Proximal Tubule Transport

Concentration of Inulin in the Nephron Tubule

The concentration of inulin along the nephron tubule is an index of water reabsorption. Inulin is freely filtered; thus, its concentration in Bowman's space is the same as it is in the plasma. Because water is reabsorbed but inulin is not, the concentration of inulin increases throughout the nephron. The greater the water reabsorption, the greater the increase in inulin concentration.

Since 2/3 of the water is reabsorbed in the proximal tubule, the inulin concentration should triple TF/P = 3.0. Its concentration should further increase in the descending limb of the loop of Henle, distal tubule, and the collecting duct (assuming ADH is present).

The segment of the nephron with the highest concentration of inulin is the terminal collecting duct.

The segment of the nephron with the lowest concentration of inulin is Bowman's space.

THE LOOP OF HENLE

Fluid entering the loop of Henle is isotonic (300 mOsm/L), but the volume is only a third of the volume originally filtered into Bowman's space. The loop of Henle acts as a countercurrent multiplier and as such creates a medullary interstitial osmolar gradient. The osmolarity can reach a maximum of about 1200 mOsm/L at the tip of the medullary interstitium in antidiuresis. The accumulation of both NaCl and urea contribute to this gradient. The major movements and consequences of this system are illustrated in Figure VIII-4-3. Numbers indicate fluid osmolarity.

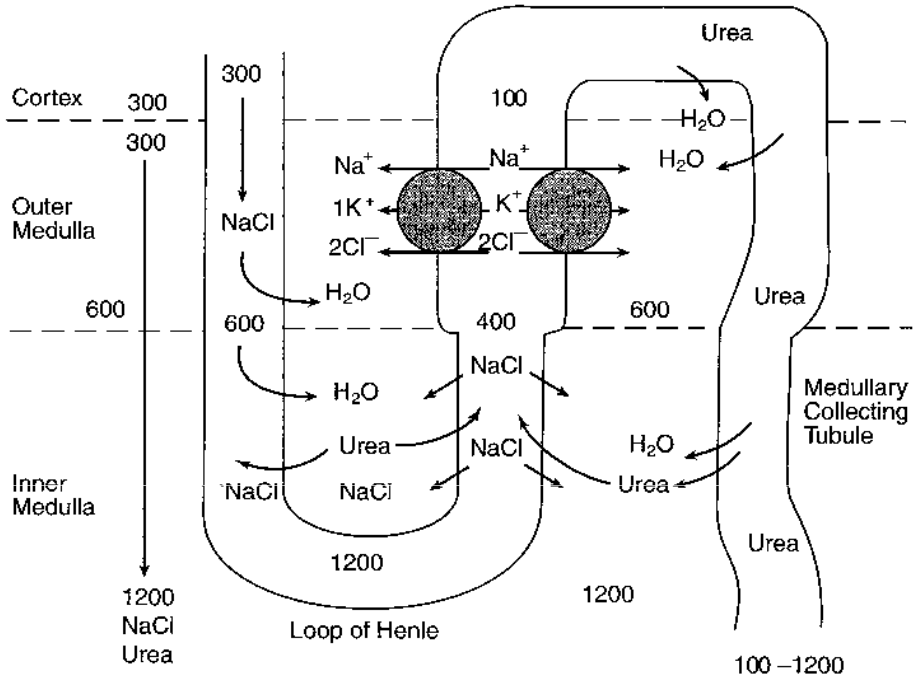


Figure VIII-4-3. Countercurrent and the Loop of Henle

One of the functions of the loop of Henle is to act as a countercurrent multiplier and create the osmolar gradient in the medullary interstitium.

The following characteristics are required for the loop of Henle to act as a countercurrent multiplier. Any disruption of these characteristics will diminish the osmolarity of the medullary interstitium and decrease the ability of the kidney to form a concentrated urine.

Countercurrent flow: opposite directional flow

Descending limb permeable to water: water diffuses into the hyperosmolar medullary interstitium, and the osmolarity of the tubular fluid in the descending loop of Henle increases, reaching a maximum at the tip of the loop of Henle. This point represents the highest osmolarity of any nephron segment. The osmolarity at the end of the collecting duct can equal this value, but only with maximum ADH effect. The descending limb is much less permeable to solute and very little is reabsorbed in this segment.

Ascending limb must be impermeable to water but must reabsorb electrolytes: an active process in the thick ascending limb (see following figure). As the sodium is removed from the ascending limb, tubular fluid osmolarity decreases to the extent that the fluid leaving the loop of Henle is hypotonic (100–150 mOsM). This is where there is a major separation between water and electrolyte reabsorption. The ascending limb is referred to as the diluting segment of the nephron.

Slow flow: flow through the loop is relatively slow. This is also a characteristic of flow through the capillary loops (vasa recta). Increased tubular fluid flow diminishes the ability of the loop to generate and maintain the osmolar interstitial gradient. Increased flow through the vasa recta washes out the metabolites. Loss of the high medullary osmolarity reduces the ability of the kidneys to form a concentrated urine. For example, if the proximal tubule fails to reabsorb two-thirds of the fluid and electrolytes filtered, the excessive load will overwhelm the loop of Henle. ADH will then be ineffective in forming a concentrated urine.

Overall the loop of Henle reabsorbs about 25% of the filtered electrolytes, which include Na^+, Cl^-, K^+, Ca^{++} and HCO_3^-. About 15% of the filtered water is also reabsorbed here. Again this is powered by the Na/K-ATPase located on the basolateral membrane. Ion movements in the thick ascending limb are shown in the following figure.

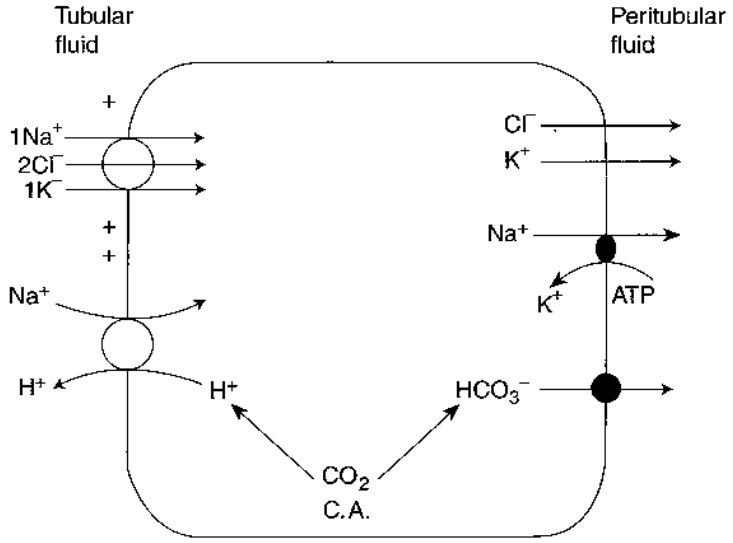


Figure VIII-4-4. Loop of Henle

On the luminal membrane Na enters the cell passively via the Na-K-2Cl symporter. The positive charge of the luminal fluid created by the Na/K-ATPase pump also facilitates this passive uptake. Increasing the basolateral pumping of sodium would increase this positive charge and transport by the symporter. Bicarbonate absorption continues here via a Na-H antiporter as was illustrated for the proximal tubule.

DISTAL TUBULE AND COLLECTING DUCT

Early distal tubule reabsorbs Na, Cl, and Ca. The NaCl crosses the apical membrane via a Na-Cl symporter. The Na is pumped across the basal membrane via the Na/K-ATPase proteins and the Cl diffuses down its electrochemical gradient through channels. This section is impermeable to water. Thus osmolarity decreases further.

Calcium transport is similar throughout the nephron. Calcium enters the cell from the luminal fluid passively through calcium channels. It is actively extruded into the peritubular fluid via Ca++-ATPase or a 3Na+-Ca++ antiporter.

Transporters in the distal tubule are summarized in Figure VIII-4-5.

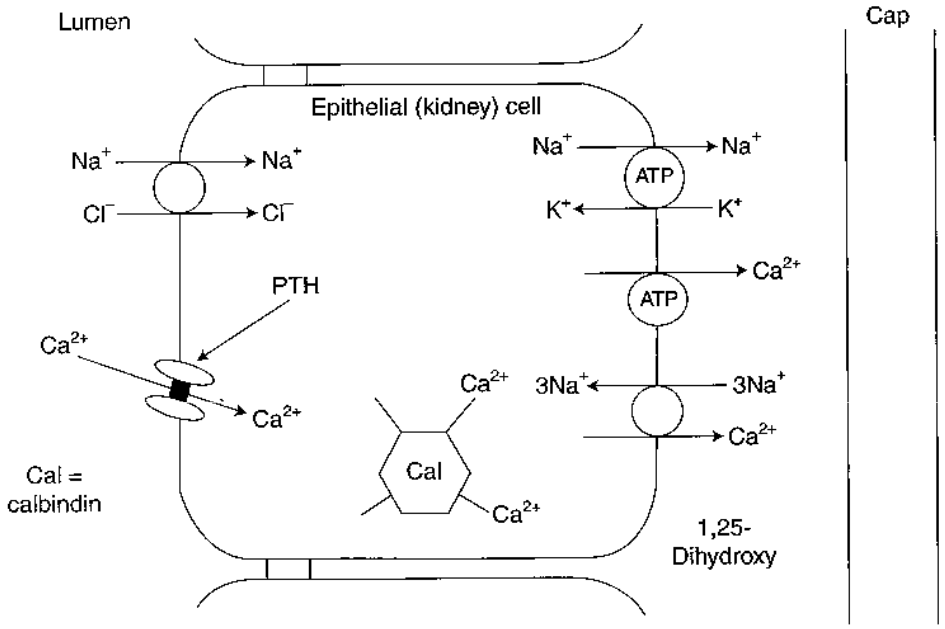


Figure VIII-4-5. Transporters in Distal Tubule

Late distal tubule and collecting duct are similar. They are composed of principal cells and intercalated cells.

Principal cells reabsorb sodium with some chloride and water. They secrete potassium.

Intercalated cells are represented by 2 different populations of cells. Some secrete H+ and in doing so generate brand new bicarbonate, which is secreted into the circulation. The second population secretes bicarbonate into the lumen of the tubule. Both are involved in acid–base regulation. This is the section of the nephron responsible for eliminating fixed acids produced by body metabolism.

Figure VIII-4-6 illustrates the net results of the principal and intercalated cells ion transports. This figure will also be used in subsequent sections to illustrate specific aspects of acid-base and electrolyte disturbances.

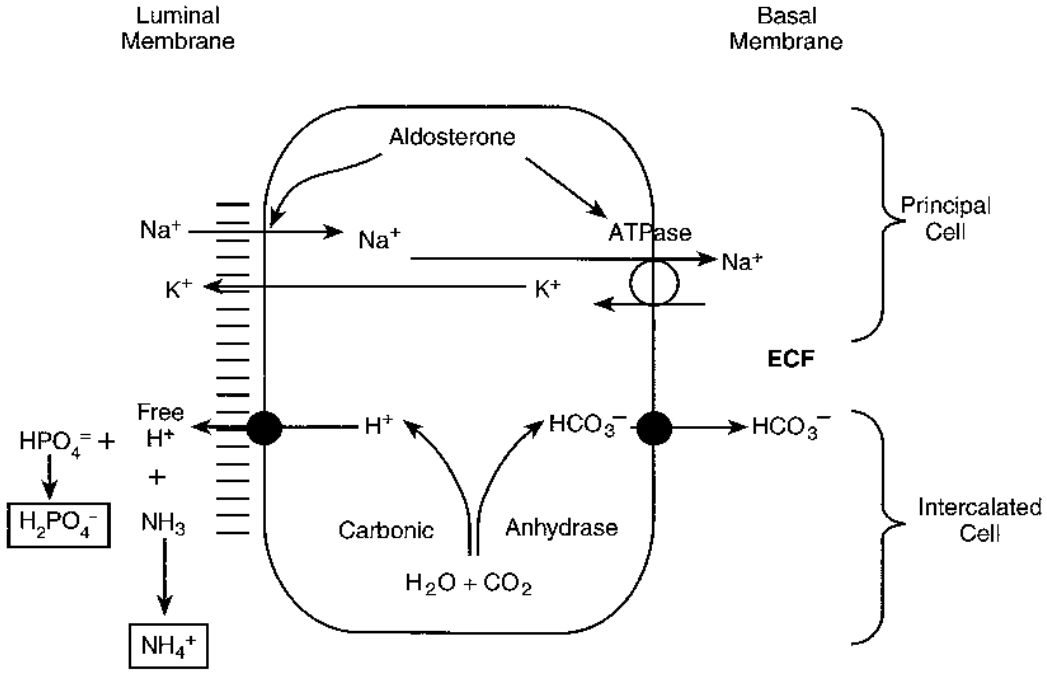


Figure VIII-4-6. Late Distal Tubule and Collecting Duct

Sodium crosses the luminal membrane passively through selective sodium channels. It is actively pumped by Na/K-ATPase in exchange for potassium (3 Na,2K) across the basal membrane. Some chloride does not follow the sodium from the luminal fluid, which gains a negative charge. This negative charge creates a net potassium secretion.

Aldosterone affects the preceding and this will be discussed in detail in Section X, Endocrinology.

Sodium and Potassium

Active sodium reabsorption is stimulated by aldosterone. The passive transport of sodium across the luminal membrane is also promoted by aldosterone (inserts channels in luminal membrane).

Net Secretion of H^+ and Acidification of the Urine

The amount of fixed acid generated by an individual is mainly determined by diet. A high percentage of animal protein in the diet generates more fixed acid than a vegetarian-based diet. The fixed acid is neutralized by plasma bicarbonate and the generation of an equivalent amount of bicarbonate in the distal nephron prevents a metabolic acidosis.

Hydrogen ions are actively secreted into the tubular lumen by two mechanisms. However, very few are excreted as free ions. Almost all are buffered mainly with phosphate or combined with ammonia.

Phosphate buffer system

Monohydrogen phosphate is freely filtered and not completely reabsorbed. The remaining amount will buffer a fraction (approximately 33%) of the secreted hydrogen ions. Availability of phosphate largely depends on the excess provided in the diet. This can be considered the first line of buffering.

Formation of ammonium

To excrete the remaining hydrogen ions, the kidney manufactures ammonia from glutamine. It simply produces what is necessary to complete the buffering process (normally about 66%).

Forms of H^+ in the urine

The H^+ in the urine will be in two main forms:

$H_2PO_4^-$, dihydrogen phosphate, also called titratable acid

NH_4^+, ammonium, also called nontitratable acid

The net loss of H^+ in the urine is simply the sum of the titratable acid and the nontitratable acid.

The net excretion of one H^+ results in the reabsorption of one HCO_3^-. This represents new HCO_3^- added to body stores. It is a net gain in HCO_3^- only because the secreted H^+ is excreted in the urine.

Total net loss of acid = net gain of new HCO_3^-

RENAL TUBULAR ACIDOSIS

Renal Tubular Acidosis Type II

- Due to a diminished capacity of the proximal tubule to reabsorb bicarbonate.
- Transient appearance of bicarbonate in the urine until the filtered load is reduced to match the reduced capacity of reabsorption.
- Steady-state characterized by a low plasma bicarbonate and an acid urine.
- An example would be Fanconi syndrome, which involves a general defect in the proximal tubular transport processes and carbonic anhydrase inhibitors.

Renal Tubular Acidosis Type I

- Due to an inability of the distal nephron to secrete and excrete fixed acid, thus an inability to form an acid urine. Urine pH > 5.5 – 6.0
- Mechanisms would include impairment of the transport systems for hydrogen ions and bicarbonate and an increased permeability of the apical membrane allowing the back diffusion of the hydrogen ions from the tubular lumen.
- The result would be a metabolic acidosis with an inappropriately high urine pH.

DISORDERS OF POTASSIUM HOMEOSTASIS

Potassium Balance

To keep the body amount constant, excretion of potassium must match dietary intake, and the kidneys regulate potassium excretion. A small percentage of ingested potassium is lost in the stool but this is not a major regulatory route under normal conditions.

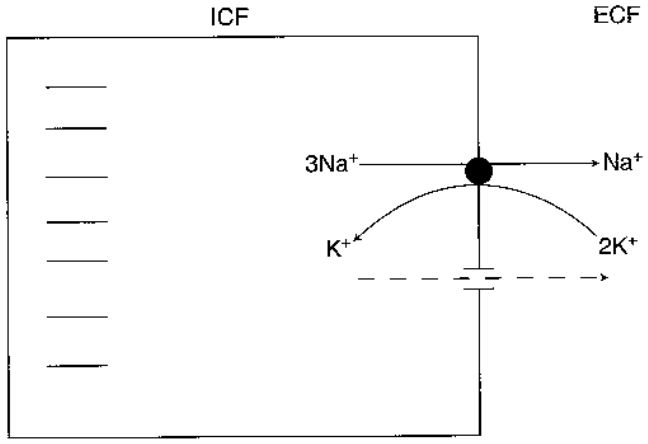


Figure VIII-4-7. ICF and ECF Potassium Distribution.
The large concentration gradient is due to membrane potential and cell membrane permeability to potassium.

- 98% of potassium inside cells (150 mEq/L)
- 2% of potassium in ECF (4 mEq/L)
- >5.0 mEq/L = hyperkalemia
- < 3.5 mEq/L = hypokalemia
- The large concentration gradient across the cell membrane is mainly due to the negative intracellular potential and the permeability of the cell membrane to potassium.
- The Na/K-ATPase pump maintains the membrane potential as well as a small net diffusion gradient from the ICF to the ECF.
- Following a meal, a significant rise in ECF is prevented by pumping potassium into non-vital tissues. This is mainly via insulin and epinephrine (β_2).
- Long term, balance is maintained via aldosterone's effect on potassium secretion in the distal tubule and collecting ducts of the nephrons.
- Acidosis and increased ECF osmolarity (cell shrinkage) shifts potassium from the ICF to the ECF. Inorganic fixed acid > organic acids > respiratory acidosis
- Alkalosis and decreased ECF osmolarity (cell swelling) shifts potassium from the ECF to the ICF. Metabolic alkalosis > respiratory alkalosis

Potassium secretion and excretion by the kidney

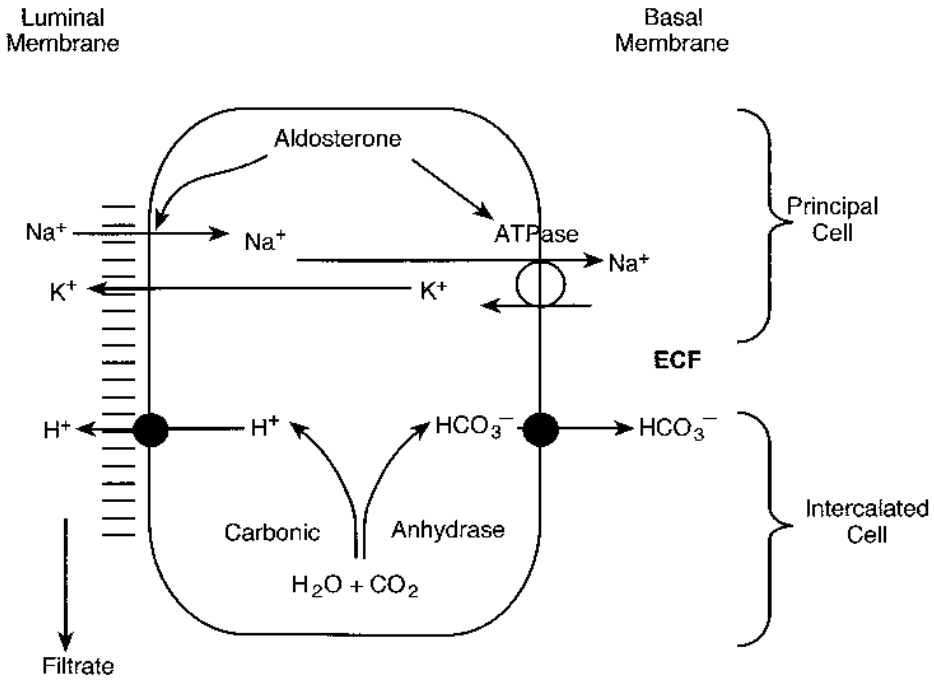


Figure VIII-4-8. Late Distal Tubule and Collecting Duct

- Potassium secretion is determined mainly by two factors: filtrate flow and the negative potential of the lumen of the distal tubule/collecting duct region.
- Increased flow and/or more negative potential increases potassium secretion and excretion.
- Decreased flow and/or less negative potential decreases potassium secretion and excretion.

Acid–Base Disorders

Acidosis: shifts potassium from the ICF to ECF. Increased hydrogen pumping in DT/CD decreases lumen potential and decreases potassium secretion (both promote hyperkalemia)

Alkalosis: shifts potassium from ECF to ICF. Reduced hydrogen pumping and increased excretion of bicarbonate increases lumen potential and increases potassium secretion (all promote hypokalemia).

Summary

Promoters of hyperkalemia

1. Transcellular shifts: metabolic acidosis, hyperglycemia, insulin deficiency or resistance, muscle trauma
2. GI: excessive intake (on rare occasions)
3. Kidney: acute oligouric kidney disease, chronic kidney disease where GFR decreased dramatically from normal, hypoaldosteronism

Consequences of hyperkalemia

1. Neuromuscular function: muscle weakness, general fatigue
2. Cardiac: high T wave, low ST segment, eventually in severe hyperkalemia ventricular fibrillation
3. Metabolic: metabolic acidosis

Promoters of hypokalemia

1. Transcellular shifts: metabolic alkalosis, sudden increases in insulin and catecholamines
2. GI: diarrhea, vomiting, low potassium diet (rarely has an effect on its own)
3. Kidney: diuretics due to increased flow (thiazides, loop diuretics, osmotic diuresis), hyperaldosteronism (adrenal adenoma, renal arterial stenosis), increased excretion of negative ions (bicarbonate, ketone bodies), renal tubular acidosis types I and II.

Consequences of hypokalemia

- Neuromuscular function: muscle weakness, general fatigue
- Cardiac: hyperpolarization affects excitability and delays repolarization.
- EKG effects: low T wave, high U wave, low ST segment
- Metabolic: decreased insulin response to carbohydrate load, decrease growth rate in children, nephrogenic diabetes insipidus, metabolic alkalosis

OVERVIEW OF RENAL FAILURE

Categorization of renal dysfunction based on location and cause:

Prerenal originate because of a hypoperfusion of kidney, e.g., structural lesions of the renal vasculature, generalized hypotension, drug effects on nephron perfusion.

Intrarenal originate from direct damage to the nephron system, either the glomerulus or the nephron itself.

Postrenal originate from urinary tract obstruction, e.g., kidney stones, prostate enlargement or spasm.

Renal Functions Affected

Elimination of waste products

Uremia (↑BUN, ↑creatinine)—Urea and creatinine are themselves nontoxic but function as indices of the accumulation of toxic waste products of metabolism. Uremia is a syndrome with specific clinical manifestations including vomiting, dyspnea, headache, and leading to, if untreated, convulsions and coma.

Salt and water balance

Inability to regulate sodium and water excretion. This can lead to hyponatremia and volume overload as well as hypernatremia and volume depletion very quickly following vomiting and diarrhea. An inability to regulate potassium excretion leads to hyperkalemia.

Acid–base regulation

A reduction in the ability to excrete fixed acid end products of metabolism leads to a metabolic acidosis and a widening of the anion gap.

Hormonal secretion

Hypocalcemia due the failure to activate vitamin D

Anemia due to lack of erythropoietin

Vascular consequences due to altered renin release

Acute Renal Failure

It is a rapid loss of renal function and results in the accumulation of waste products in the blood that are normally excreted by the kidney (↑BUN, ↑creatinine)

Prerenal: decreased renal perfusion as would occur with a decreased renal perfusion pressure, e.g., hypovolumia of hemorrhage, diarrhea, vomiting; congestive heart failure

Initially no renal injury and reversible if corrected early.

Intrarenal: glomerulonephritis, interstitial nephritis, ischemia, rhabdomyolysis, sepsis. Tends to quickly lead to acute tubular necrosis

Postrenal: obstruction of the outflow tract

All eventually lead to acute tubular necrosis, which is a direct tubular damage. Tubular cells lose their ability to attach to other cells and many slough into the filtrate and appear in the urine. It may be reversible or irreversible depending on the extent and duration of injury.

Chronic Renal Failure

- In acute renal failure the nephrons can in many cases recover from the sloughing of the tubular epithelial cells.
- In chronic renal failure there is an irreversible loss of nephrons. The remaining nephrons, in order to compensate, have an increase in glomerular capillary pressure and hyperfiltration. One way of looking at this is a "hypertension" at the level of the nephron. The hyperfiltration combined with the increased work load promotes further injury leading to fibrosis, scarring, and loss of additional nephrons.
- Chronic renal failure is categorized based on the level of GFR and the presence or absence of proteinuria.
- When GFR decreases to about 20% of normal the BUN starts to rise but the patients may still be asymptomatic.
- Most patients have some sodium and water retention. This can lead to hypertension, congestive heart failure, and peripheral edema.
- Compensatory increases in aldosterone initially prevent hyperkalemia but beyond a certain point this becomes a problem.
- Additionally, phosphate retention and loss of vitamin D activity cause a secondary hyperparathyroidism and bone loss; anemia is due to loss of erythropoietin.

Diabetic Nephropathy

- Diabetes is the most common cause of chronic renal failure.
- Characterized by proteinuria, glomerular lesions that are associated with eventual capillary collapse, glomerulosclerosis, and loss of GFR.
- Hyperglycemia and insulin deficiency play a major role in diabetic nephropathy at least in the development of "nephron hypertension" and hyperfiltration.
- In many instances the patient begins with an above-normal GFR.
- The first sign of renal disease is microalbuminuria.
- As GFR decreases the proteinuria increases.

Chapter Summary

* In the proximal tubule, two-thirds of the water and electrolytes are reabsorbed, along with almost all the organic molecules filtered. An exception is urea. Because equal amounts of solutes and fluid are reabsorbed, the fluid remains isotonic.
* The loop of Henle, acting as a countercurrent multiplier, creates an osmotic gradient in the medullary interstitium, with the tip reaching a maximum of 1200 mOsm/L. This value determines the maximum osmolarity of the urine. Because the descending limb is permeable to water, tubular osmolarity increases in this limb. Because the ascending limb is impermeable to water and sodium chloride is reabsorbed, osmolarity decreases in this limb, and the tubular fluid leaves hypotonic.
* In the early distal tubule additional electrolytes are reabsorbed and the osmolarity decreases further. In the late distal tubule and collecting duct aldosterone regulates the final electrolyte modifications and ADH the final osmolarity.
* Net acid lost in the urine is via phosphate and ammonium. Renal tubular acidosis is a metabolic acidosis caused by a failure of nephron cellular processes. Proximal failure is type II and distal failure (distal tubule/collecting duct) is type I.
* Hyperkalemia can be caused either by a transcellular shift in potassium (ICF to ECF) or a failure of the kidney to excrete adequate amounts of potassium.
* Hypokalemia can be caused by a transcellular shift in potassium (ECF to ICF) or to excess loss via the GI tract or kidney.
* Hyper- and hypokalemia affect the excitability of the neuromuscular system including cardiac muscle.
* Acute renal failure (disease) is a sudden loss of renal function (GFR) and is reversible.
* Chronic renal failure (disease) is a loss of functioning nephrons and is generally not reversible. Diabetes is the major cause of chronic renal failure followed by hypertension.

SECTION IX

Acid–Base Disturbances

Acid–Base Disturbances

THE BUFFERING SYSTEMS

Specific disturbances in the system regulating H^+ can be illustrated by using the equation in Figure IX-1-1, which represents the bicarbonate buffer system with all other buffer pairs represented as HBuf/Buf^-.

The purpose of the regulating system is to control the concentration of H^+ ions, and the concentrations of other elements are of importance only in how they affect H^+ concentration.

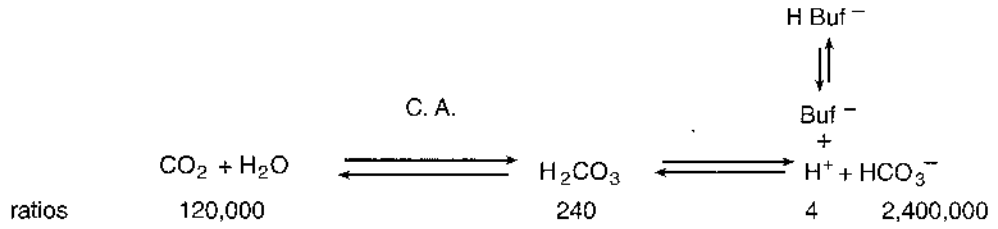


Figure IX-1-1. Production of Carbonic Acid

To demonstrate the changes in the major variables during acid–base disturbances, the scheme can be simplified to the following:

$$CO2 \leftrightarrow H^+ + HCO3^-$$

A disturbance causes a shift and, in doing so, affects the H^+ concentration, measured as a change in pH (increase H^+ = decrease pH).

THE FOUR PRIMARY DISTURBANCES

Four primary disturbances in the system are recognized, each of which results in an altered concentration of H+. The basic deviations from normal can be either an acidosis (excess H+) or an alkalosis (deficiency of H+), which in either case may be caused by either a respiratory or a metabolic problem. In many texts the pH change in the arterial blood is referred to as an acidemia or an alkalemia and the process that induced the change an acidosis or an alkalosis.

Respiratory Acidosis

Caused by a decrease in alveolar ventilation relative to the total body production of CO_2 (hypoventilation). The result is an increase in PCO_2, which causes an increase in H+ (or decrease in pH) and an increase in HCO_3^-. Note that for every H+ produced during the development of respiratory acidosis, one HCO_3^- is also produced. Some rise in HCO_3 will always occur in uncompensated respiratory acidosis. But in most cases, the HCO_3^- will not rise out of its normal range. Quantitatively for every 10 mm Hg rise in $PaCO_2$, the HCO_3^- will rise about 1 mM/L and the pH should fall by 0.08 pH units.

Respiratory acidosis can be caused by the following:

- Respiratory center depression (anesthetics, morphine)
- Pulmonary edema, cardiac arrest
- Airway obstruction
- Muscle relaxants
- Sleep apnea
- Chronic obstructive lung disease
- Restrictive lung diseases
- Neuromuscular defects (multiple sclerosis, muscular dystrophy)
- Obesity hypoventilation syndrome

Summary

Cause: increase in $PaCO_2$

Result: decrease in pH, slight increase in HCO_3^-

Respiratory Alkalosis

Caused by an increase in alveolar ventilation relative to body production of CO_2 (hyperventilation). The decrease in CO_2 causes a decrease in H+ (increased pH) and a decrease in HCO_3^-. Note that for every H+ consumed, one HCO_3^- is also consumed. Some decrease in HCO_3^- will always occur in uncompensated respiratory alkalosis. Quantitatively for every 10 mm Hg decrease in PaCO2 the HCO_3^- will decrease about 2 mM/L and the pH should rise 0.08 pH units.

Respiratory alkalosis can be caused by:

- Anxiety
- Fever
- Hypoxemia
- Pneumothorax (in some cases)
- Ventilation–perfusion inequality
- Hypotension
- High altitude

Summary

Cause: decrease in $PaCO_2$

Result: decrease in H^+ (increased pH)

Slight decrease in HCO_3^-

With the preceding respiratory problems, the cause originated with CO_2 on the left side of the equilibrium reaction. With a metabolic problem, the cause originates on the right side of the reaction. However, the cause can be a consequence of a direct change in either H^+ or HCO_3^-. A gain in H^+ as fixed acid (i.e., one not due to a respiratory effect) is equivalent to the direct loss of HCO_3^-. Either change will produce the same overall effect on H^+ (or pH). This section looks at the consequences of a metabolic disorder as a gain or loss of H^+, but an equally correct approach would be looking at a loss or gain of HCO_3^-. In fact, although both produce acidosis, net addition of nonvolatile acid differs in some respects from loss of bicarbonate without gain of acid. The two causes of acidosis can in many cases be distinguished by considering the plasma anion gap, discussed later in this section, and the plasma chloride concentration.

Also, there is a greater change in HCO_3^- in an uncompensated metabolic disturbance than in an uncompensated respiratory disturbance.

Metabolic Acidosis

Caused by a gain in fixed acid. The increased H^+ forces the reaction to the left, decreasing HCO_3^-. Forcing the reaction to the left will produce some CO_2, but, by convention, if there is no respiratory compensation for the metabolic problem, no significant change in arterial PCO_2 is considered to have taken place.

There are three main causes of a metabolic acidosis:

1. Increased acid production, e.g., lactic acidosis, ketoacidosis
2. Bicarbonate loss in renal tubular acidosis (RTA) type II and diarrhea
3. Decreased ability of the nephron to excrete fixed acid and thus failure to add new bicarbonate to body stores. Acute and chronic renal disease (or failure), inability of the nephron to synthesize ammonia, and RTA type I

Summary

Cause: gain in H^+ as fixed acid (or a loss in HCO_3^- via GI tract or kidney)

Result: decrease in pH and HCO_3^-

Metabolic Alkalosis

Caused by a loss of fixed acid. The decreased H^+ forces the reaction to the right, increasing HCO_3.

It is a primary rise in plasma bicarbonate with the associated rise in arterial pH.

The condition is defined by two separate processes: generation of the disturbance and maintenance, i.e., a paradoxical response by the kidney, preventing the excretion of the excess bicarbonate.

Generation:

- Vomiting or gastric suctioning
- Loop and thiazide diuretic use
- Barter and Gitelman syndromes
- Intracellular shift of hydrogen ions as in hypokalemia
- Primary hyperaldosteronism
- Loss of bicarbonate-free fluid (contraction alkalosis)

Maintenance:

Volume depletion, increased aldosterone, chloride depletion, and hypokalemia all can contribute to a diminished ability of the nephron to excrete bicarbonate and return arterial pH to normal.

Summary

Cause: loss in H^+ as fixed acid (or a gain in HCO_3^-)

Result: increase in pH and HCO_3^-

DIAGNOSING THE PROBLEM

Summary of the changes in the uncompensated state:

$$CO_2 \leftrightarrow H^+ + HCO_3^-$$

Table IX-1-1. Summary of the Changes in the Uncompensated State

	CO_2	pH	HCO_3^-
Respiratory acidosis	↑	↓	↑
Respiratory alkalosis	↓	↑	↓
Metabolic acidosis	no change	↓	↓↓
Metabolic alkalosis	no change	↑	↑↑

Understanding the preceding is key to diagnosing an underlying disturbance. The disturbance should be determined first; then, compensatory mechanisms can be evaluated. A specific method of analyzing the data available must be developed. The following is one scheme that works well to determine the underlying disturbance(s).

Normal Systemic Arterial Values

pH = 7.4 PCO_2 = 40 mm Hg HCO_3^- = 24 mmol/L

Formulation of a Diagnosis

To formulate a diagnosis of the problem(s), one of the two possible pathways is followed, either acidosis or alkalosis.

Table IX-1-2. Summary of Acid–Base Disorders

	Acidosis	Alkalosis
pH	Low	High
Respiratory Component: PCO_2	High	Low
Metabolic Component: HCO_3^-	Low	High

Acidosis

- If the pH is depressed, it is an acidosis.
- If the CO_2 is elevated, there is a respiratory component to the acidosis (but it could also include a metabolic component).
- If there is an acidosis and the CO_2 is not elevated, the only possible explanation is the presence of a metabolic acidosis (bicarbonate must be reduced).
- If the CO_2 is elevated and the bicarbonate is depressed, it is a combined respiratory and metabolic acidosis.

Alkalosis

- If the pH is elevated, it is an alkalosis.
- If the CO_2 is depressed, there is a respiratory component to the alkalosis (but it could also include a metabolic component).
- If there is an alkalosis and the CO_2 is not depressed, the only possible explanation is the presence of a metabolic alkalosis (bicarbonate must be elevated).
- If the CO_2 is depressed and the bicarbonate is elevated, it is a combined respiratory and metabolic alkalosis.

Combined disturbances

If the CO_2 and HCO_3^- change in opposite directions, it is a combined disturbance. It is either a combined respiratory and metabolic acidosis or a combined respiratory and metabolic alkalosis.

COMPENSATORY MECHANISMS

Compensation can be via the respiratory system and/or the kidneys.

$$CO_2 \leftrightarrow H^+ + HCO_3^-$$

respiratory	renal
variable	variable

Respiratory Compensation

This will occur only in a metabolic disturbance and can begin almost immediately.

- Metabolic acidosis: compensation is a hyperventilation. The hyperventilation reduces CO_2, shifting the reaction to the left and consuming H^+. The expected PCO_2 can be determined using Winter's formula. Expected $PCO_2 = 1.5(HCO_3^-) + 8$
- Metabolic alkalosis: compensation is a hypoventilation. The hypoventilation increases CO_2, shifting the reaction to the right and producing H^+. Expected rise in PCO_2 should be about .7 mm Hg for each 1 mEq/L rise in HCO_3^-.

Renal Compensation

This can occur in a respiratory and/or metabolic disturbance. However, if the kidney is the source of the metabolic disturbance, only respiratory compensation will be significant. The kidney has the ability to change plasma bicarbonate. To lower plasma bicarbonate, the kidney excretes HCO_3^- in the urine. To raise plasma bicarbonate, the kidney has the capability to generate new HCO_3^- (distal tubule collecting duct) and secrete it into the general circulation. Renal compensation is slower than respiratory compensation, taking days to fully develop.

- **Acidosis**—compensation is HCO_3 production by the kidney and its secretion into the circulation. This will shift the reaction to the left and consume H^+. During renal compensation, plasma HCO_3^- should slowly increase and the H^+ will be excreted in the urine (acid urine). In chronic respiratory acidosis that has been present for at least 4-5 days the accompanied increase in HCO_3^- should be about .4 times the increase in PCO_2.
- **Alkalosis**—compensation is HCO_3^- excretion (alkaline urine). This will shift the reaction to the right and generate H^+. During renal compensation, plasma HCO_3^- should slowly decrease. In chronic respiratory alkalosis that has been present for at least 4-5 days, the accompanied decrease in HCO_3^- should be about .4 times the decrease in PCO_2.

EXAMPLES OF DISTURBANCES

1.	Arterial	pH	7.3	metabolic acidosis
		PCO_2	30 mm Hg	
		PO_2	95 mm Hg	
	Serum	HCO_3^-	14 mEq/L	

A decrease in CO_2 below 40 means respiratory compensation via hyperventilation.

If the kidneys are functioning, they would be manufacturing HCO_3^- and secreting it into the plasma, and the individual would be forming a very acid urine.

2.	Arterial	pH	7.6	respiratory alkalosis
		PCO_2	20 mm Hg	
		PO_2	95 mm Hg	
	Serum	HCO_3^-	18 mEq/L	

If the kidneys are functioning, they would be dumping HCO_3^- in the urine, and the individual would be forming an alkaline urine.

3.	Arterial	pH	7.2	respiratory acidosis
		PCO_2	80 mm Hg	
		PO_2	70 mm Hg	
	Serum	HCO_3^-	30 mEq/L	

If the kidneys are functioning, they would be manufacturing HCO_3^- and secreting it into the plasma, and the individual would be forming a very acid urine.

4.	Arterial	pH	7.6	metabolic alkalosis
		PCO_2	52 mm Hg	
		PO_2	70 mm Hg	
	Serum	HCO_3^-	44 mEq/L	

An increase in CO_2 above 40 means respiratory compensation via hypoventilation.

If the kidneys are functioning, they would be dumping HCO_3^- in the urine, and the individual would be forming an alkaline urine.

5.	Arterial	PCO_2	55 mm Hg	combined respiratory and metabolic acidosis
	Serum	HCO_3^-	20 mEq/L	

The only possible compensation would be via the kidney. If the kidneys are functioning, they would be manufacturing HCO_3^- and secreting it into the plasma, and the individual would be forming a very acid urine.

PLASMA ANION GAP (PAG)

- The total cation charges in the plasma always equal the total anion charges present. However, only major ions are measured when calculating the anion gap. The anion gap is simply due to unmeasured anions.
- Cations are estimated as the plasma concentration of the major cation, Na^+. It is not usually the case but some clinicians also include K^+.
- Anions are estimated as the plasma Cl^- and HCO_3^-.

Normal Values

$Na^+ = 140$ mEq/L $\quad Cl^- = 108$ mEq/L $\quad HCO_3^- = 24$ mEq/L

$PAG = Na^+ - (Cl^- + HCO_3^-)$ $\quad PAG = 8$

This leads to a normal anion gap of about 10 ± 2 mEq/L. The negative charges on the protein anions account for most of the anion gap. Thus, the normal anion gap must be adjusted downward in hypoalbuminemia.

The anion gap is most useful in diagnosing the cause of a metabolic acidosis. The anion gap will increase in these states when there is the accumulation of anions generated by the acidosis other than chloride. In most cases these will include organic anions; e.g., lactic acidosis, ketoacidosis (diabetes), and the ingestion of salicylate, ethylene glycol, alcohol, and methanol.

Anion gap is not elevated if the primary disorder is due to loss of bicarbonate, e.g., diarrhea, RTA, types I and II. Excess chloride is reabsorbed. In RTA type I the situation is slightly different but there is no widening of the anion gap. The net result is a hyperchloremic metabolic acidosis. However, with acute and chronic renal failure the retention of both the H^+ and the anions such as sulfate, phosphate, and urate will cause a widening of the anion gap.

The most important point to remember is that there is no widening of the anion gap in diarrhea, RTA types I and II. All other causes of a metabolic acidosis will promote a widening of the anion gap.

GRAPHICAL REPRESENTATION

The quantitative changes that occur in the acid–base homeostatic system can be represented graphically by the Davenport diagram. The pH units are plotted on the *x* axis, and HCO_3^- concentration on the *y* axis. Any point on this graph representing a given pH and HCO_3^- has a fixed value of PCO_2. This can be easily seen by referring to the Henderson-Hasselbalch equation.

$$pH = pK + \log \frac{[HCO_3^-]}{aPCO_2}$$

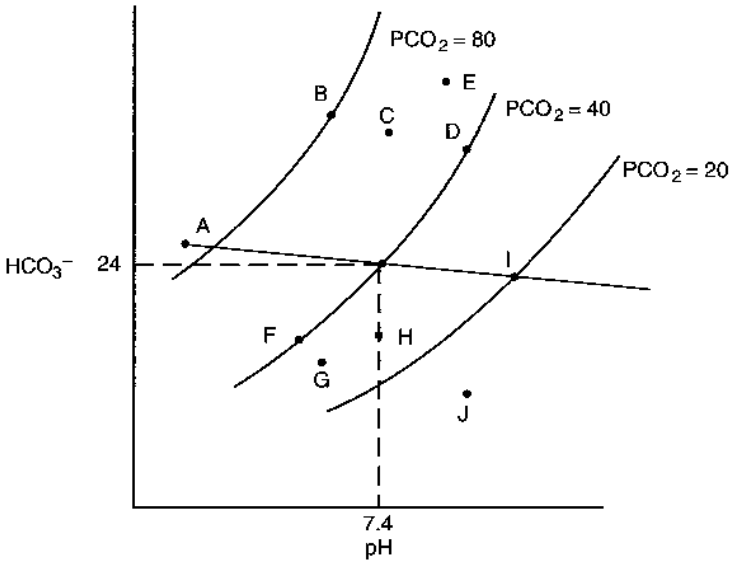
$pK = 6.10$ $\quad$ $[HCO_3^-]$ in mmol/L

$a = 0.0301$ $\quad$ PCO_2 in mm Hg

When two variables are known, the third is fixed and can be calculated:

For example, if pH = 7.4 and $HCO_3^- = 24$ mmol/L, then PCO_2 must be 40 mm Hg. All points can be found on the graph at which the PCO_2 must be 40 mm Hg. All points lying on the locus will form a line referred to as the PCO_2 40 mm Hg isobar. Other isobars can be drawn for other values of PCO_2.

Understanding the graph below will permit the diagnosis of all the primary disturbances.



A = uncompensated respiratory acidosis, or acute hypoventilation
B = partially compensated respiratory acidosis
C = completely compensated respiratory acidosis or completely compensated metabolic alkalosis
D = uncompensated metabolic alkalosis
E = partially compensated metabolic alkalosis
F = uncompensated metabolic acidosis
G = partially compensated metabolic acidosis
H = completely compensated metabolic acidosis or completely compensated respiratory alkalosis, or someone who has been living at a high altitude for several weeks
I = uncompensated respiratory alkalosis or acute hyperventilation, or someone who just arrived at a high altitude
J = partially compensated respiratory alkalosis, or someone in the process of acclimatization at high altitude

Figure IX-1-2. Davenport Diagram

Chapter Summary

* If the pH is depressed, it is an acidosis.
* If the CO_2 is elevated, there is a respiratory acidosis.
* If the bicarbonate is reduced, there is a metabolic acidosis.
* If the CO_2 is elevated and the bicarbonate is depressed, it is a combined respiratory and metabolic acidosis.
* If the pH is elevated, it is an alkalosis.
* If the CO_2 is depressed, there is a respiratory alkalosis.
* If the bicarbonate is elevated, there is a metabolic alkalosis.
* If the CO_2 is depressed and the bicarbonate is elevated, it is a combined respiratory and metabolic acidosis.
* Respiratory compensation is immediate but renal compensation is slower, often taking days to fully develop.
* The respiratory response to a metabolic acidosis is hyperventilation.
* The respiratory response to a metabolic alkalosis is hypoventilation.
* The renal response to an acidosis is the excretion of acid and the generation of new bicarbonate.
* The renal response to an alkalosis is the excretion of bicarbonate.
* A widening of the anion gap occurs when anions other than chloride accumulate during a metabolic acidosis. This does not occur with diarrhea or Types I and II renal tubular acidosis.
* A metabolic acidosis can originate with the kidney, or is the result of increased acid production or the loss of bicarbonate in diarrhea.
* RTA type I – decreased capacity of the distal nephron to excrete hydrogen ions; urine pH > 5.5–6.0
* RTA type II – decreased capacity of the proximal tubule to reabsorb bicarbonate; urine pH < 5.5–6.0
* Renal failure – decreased capacity of the kidney to excrete hydrogen ions because of a loss of functioning nephrons
* A metabolic alkalosis is caused by a primary rise in plasma bicarbonate and is maintained by a decreased capacity of the kidney to eliminate the excess bicarbonate.

SECTION X

Endocrinology

General Aspects of the Endocrine System

Note: Hormonal action is such a pervasive subject that information is presented in several chapters and books. As might be expected, this chapter emphasizes the physiologic action of the endocrine hormone. In contrast, the molecular action of hormones is emphasized in the biochemistry book. The properties and actions of the endocrine system and other hormones can also be found in the discussion of relevant systems throughout these books.

GENERAL CHARACTERISTICS

Lipid-Versus Water-Soluble Hormones

Figure X-1-1 demonstrates several major differences between the lipid-soluble hormones and the water-soluble hormones.

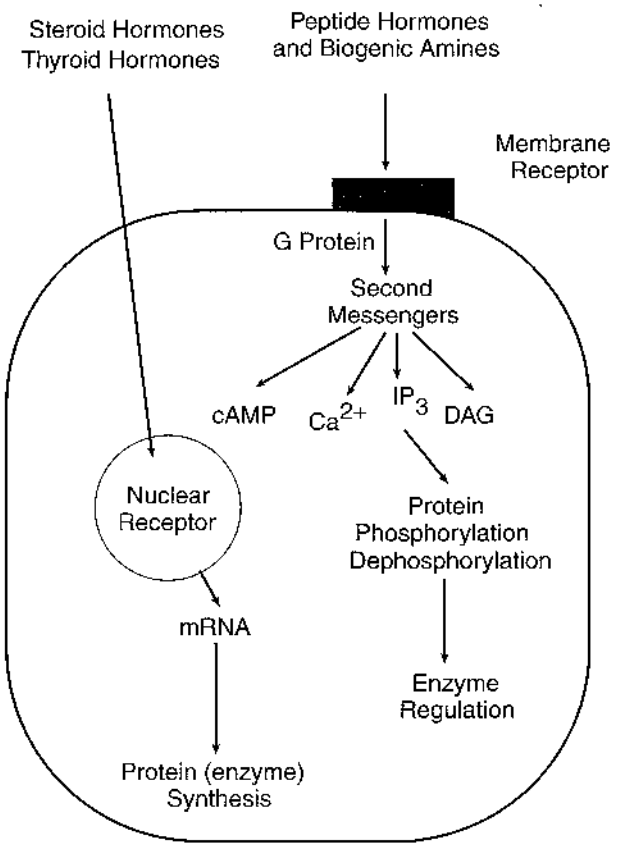
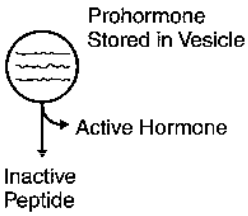


Figure X-1-1. Signal Transduction Mechanisms

Table X-1-1. Summary of the Differences Between the Two Major Classes of Hormones

	Lipid-Soluble Hormones (steroids, thyroid hormones)	**Water-Soluble Hormones** (peptides, proteins)
Receptors	Inside the cell, usually in the nucleus	Outer surface of the cell membrane
Intracellular action	Stimulates the synthesis of specific new proteins	Production of second messengers, e.g., cAMP Insulin does not utilize cAMP, instead activates membrane-bound tyrosine kinase Second messengers modify action of intracellular proteins (enzymes)
Storage	Synthesized as needed Exception: thyroid hormones	Stored in vesicles In some cases, prohormone stored in vesicle along with an enzyme that splits off the active hormone 
Plasma transport	Attached to proteins that serve as carriers Exception: adrenal androgens	Dissolved in plasma (free, unbound)
Half-life	Long (hours, days) $\propto$ to affinity for protein carrier	Short (minutes) $\propto$ to MW

Protein-Bound and Free Circulating Hormones

The liver produces proteins that bind lipid-soluble hormones, e.g.:

- cortisol-binding globulin
- thyroid-binding globulin
- estrogen/testosterone-binding globulin

Equilibrium

The lipid-soluble hormones circulating in plasma bound to protein is in equilibrium with a small amount of free hormone. It is the free form that is available to the tissues, and thus the free unbound form normally determines the plasma activity. It is the free form that also creates negative feedback. This equilibrium is shown in Figure X-1-2.

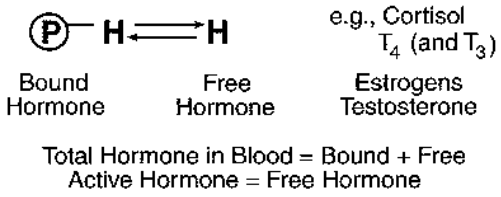


Figure X-1-2. Transport of Lipid-Soluble Hormones

Role of the liver

If the liver changes its production and release of binding proteins, the circulating level of **bound hormone will change.** However, under most conditions the level of **free hormone will remain constant.**

Modulation

Liver dysfunction and androgens can decrease and estrogens can increase the circulating level of binding proteins. For example, a rise in circulating estrogen causes the release of more binding protein by the liver, which binds more free hormone. The transient decrease in free hormone reduces negative feedback to the hormone-secreting tissue. The increased secretion of free hormone quickly returns the plasma free hormone to normal.

This explains why during pregnancy and other states with a rise in estrogen levels:

- Total plasma lipid-soluble hormone increases.
- Free plasma hormone remains constant at a normal level; thus, the individual does not show signs of hyperfunction.

PROPERTIES OF RECEPTORS

Hormone Specificity

A hormone affects only cells that possess receptors specific to that particular hormone.

For example, both adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH) increase the secretion of steroid hormones. However, ACTH does so only in the adrenal cortex and LH only in gonadal tissue.

Hormone Activity

Under normal conditions, receptors are not saturated; that is, extra receptors exist. Therefore:

- Normally, the number of hormone receptors is not rate-limiting for hormone action.
- The plasma concentration of free hormone is usually indicative of activity.

Resistance to Hormone Action (Down Regulation)

- Abnormalities in receptors or events distal to the ligand-receptor interaction, often due to chronic elevation of circulating hormone (e.g., type II diabetes) or drug therapy.
- Under these conditions receptors are often saturated.
- Reduction of hormone levels often produces some recovery in sensitivity.
- The clinical presentation is often one of normal or elevated hormone levels but with reduced or absent peripheral manifestations of the hormone and a failure of replacement therapy to correct the problem

Permissive Action

A phenomenon in which one type of hormone must be present before another hormone can act; for example, cortisol must be present for glucagon to carry out glycogenolysis and prevent hypoglycemia.

MEASUREMENT OF HORMONE LEVELS

Plasma Analysis

- Provides information at the time of sampling only and may not reflect the overall secretion rate
- When hormone secretion is episotic, single sampling may reflect peaks (erroneous hyperfunction) or nadirs (erroneous hypofunction). Pulsatile secretion, diurnal and cyclic variation, age, sleep entrainment, and hormone antagonism must all be considered in evaluating circulating levels.
  - Growth hormone is secreted in pulses and mainly at night. This is not reflected in a fasting morning sample. However, growth hormone stimulates the secretion of IGF-I which circulates attached to protein and has a long half-life (20 hours). Plasma IGF-I measured at any time during the day is usually a good index of overall growth hormone secretion.
  - Thyroid is a fairly constant system and T4 has a half-life of about 6–7 days. Thus, a random measurement of T4 is usually a good estimate of daily plasma levels.

Urine Analysis

- Restricted to the measurement of catecholamines and steroid hormones. Urine analysis of polypeptide hormones are not generally useful.
- A distinct advantage of urine analysis is that it provides an integrated sample.
  - A "24-hour urine free cortisol" is often necessary to pick up a low level Cushing's disease and to eliminate the highs and lows of the normal circadian rhythm.

DISORDERS OF THE ENDOCRINE SYSTEM

Hypofunction

- Can be caused by autoimmune disease (e.g., type 1 diabetes, hypothyroidism, adrenal insufficiency, gonadal failure), tumors, hemorrhage, infection, damage by neoplasms

- Evaluated by a stimulation test
  - Hypothalamic hormones test anterior pituitary reserve
  - Inducing hypoglycemia (via insulin injection) stimulates the release of all stress hormones (glucagon, growth hormone, cortisol, epinephrine)

Hyperfunction

- Caused by tumors, hyperplasia, autoimmune stimulation, ectopically produced peptide hormones (e.g., ACTH, ADH, calcitonin)
- Evaluated by a suppression test
  - Failure of glucose to suppress growth hormone diagnostic for acromegaly
  - Failure of dexamethazone (low dose) to suppress cortisol diagnostic for hypercortisolism
  - Multiple endocrine neoplasia (MEN) represents a group of inheritable syndromes characterized by multiple benign or malignant tumors.

    MEN 1: hyperparathyroidism, endocrine pancreas, and pituitary edenomas

    MEN 2A: medullary carcinoma of the thyroid, pheochromocytoma, hyperparathyroidism

    MEN 2B: medullary carcinoma of the thyroid, pheochromocytoma, hyperparathyroidism typically absent.

Gland Structure and Size

- When an endocrine gland does not receive its normal stimulus, it generally undergoes a reversible atrophy.
  - Long-term high doses of glucocorticoids suppress the ACTH-adrenal axis. Withdrawal of therapy can require up to a year for complete recovery.
- Overstimulation of endocrine tissue can cause cell proliferation or hypertrophy in addition to hormone overproduction.
  - In Grave's disease, overstimulation of the thyroid tissues causes cell proliferation and this polyclonal expansion creates a goiter in addition to hyperthyroidism.
- Tumors, which are generally monoclonal expansions, may also create a hyperfunction. Others produce little if any hormone but are still disease-producing because of the compressive (mass) effect of the additional tissue.

Chapter Summary

* Lipid-soluble endocrine hormones: Receptors are inside cells. Because they must be synthesized as needed and must generate new proteins to carry out their actions, they represent slow-acting systems. The total plasma level does not necessarily provide an index of activity because most is bound. It is the free hormone that determines activity.
* Water-soluble hormones: Receptors are on the membrane surface. Second messengers carry out intracellular action. Because they are stored in vesicles and need only modify proteins to carry out their actions, they are fast-acting systems.
* Normally, receptors are not saturated. It is the plasma level of free hormone that determines activity.
* Tissue resistance elevates plasma hormone levels but reduces peripheral effects.
* Plasma hormonal analysis may not reflect overall secretion rate.
* Urine analysis provides an integrated sample for catecholamines and some steroid hormones.
* Hypofunction is evaluated by a stimulation test.
* Hyperfunction is evaluated by a suppression test.
* Lack of glandular stimulation causes a reversible atrophy.
* Overstimulation of a gland can cause hypertrophy or hyperplasia.

Hypothalamic–Anterior Pituitary System

GENERAL FEATURES

- The hormones in this system are all water-soluble.
- The hypothalamic hormones are synthesized in the neuron cell body, packaged in vesicles, and transported down the axon to be stored and released from the nerve terminals.
- Pituitary is located in the bony sella turcica at the base of the skull. The arachnoid membrane (diaphragm sellae) separates it from and prevents cerebrospinal fluid from entering the sella turcica.
- Optic chiasm is 5–10 mm above this diaphragm.
- In the hypothalamic–anterior pituitary system, hormonal release is mainly pulsatile. A possible exception is the thyroid system.
- The pulsatile release of GnRH prevents downregulation of its receptors on the gonadotrophs of the anterior pituitary. A constant infusion of GnRH will cause a decrease in the release of both LH and FSH.

The hypothalamic–anterior pituitary system is summarized in Figure X-2-1.

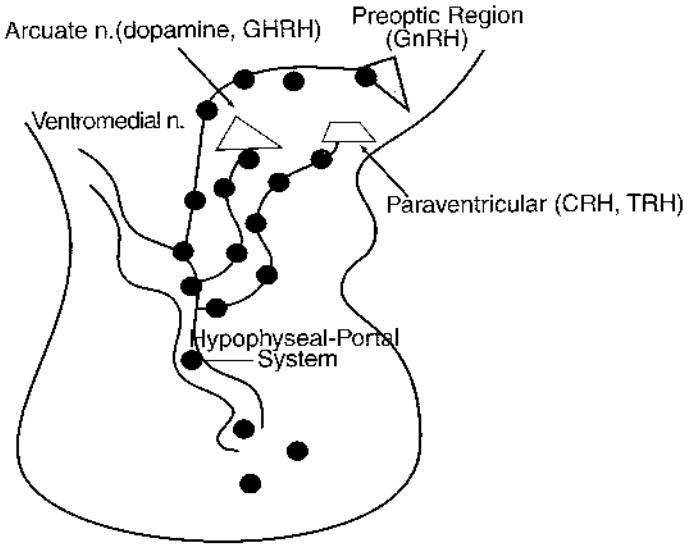
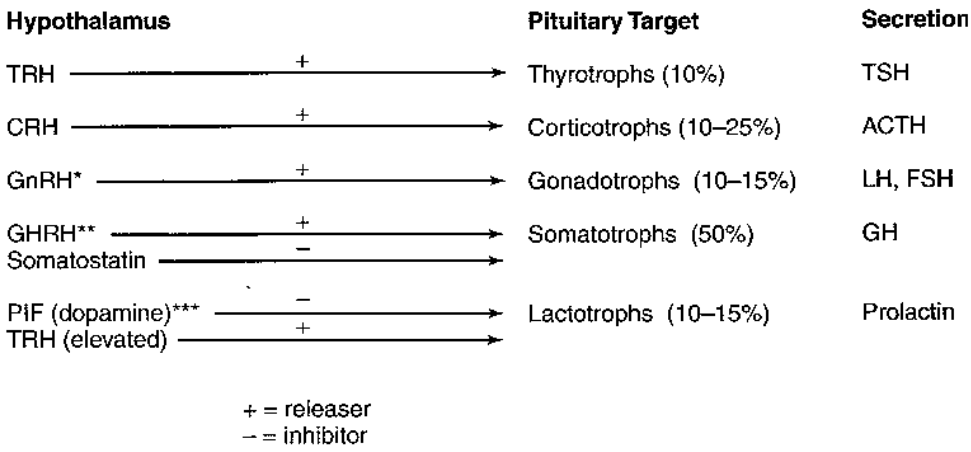


Figure X-2-1. Hypothalamic–Anterior Pituitary Axis

- The hypothalamic hormones, thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), growth hormone–releasing hormone (GHRH), somatostatin, and prolactin-inhibiting factor (PIF) are synthesized in neuronal cell bodies in the arcuate and paraventricular nuclei; gonadotropin-releasing hormone (GnRH) is synthesized in the preoptic nucleus.
- The nerve endings all come together in the median eminence region of the hypothalamus. The hormones are then secreted into the hypophyseal-portal system and transported to the anterior pituitary.
- Hypothalamic hormones bind to receptors on cells of the anterior pituitary and modify the secretion of thyroid-stimulating hormone (TSH) (thyrotropin), corticotropin (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), and prolactin.

Effect of Each Hypothalamic Hormone on the Anterior Pituitary



*High frequency pulses favor LH, low frequency pulses favor FSH

**The fact that eliminating hypothalamic input causes a decrease in growth hormone secretion indicates that GHRH is the main controlling factor.

***When the connection between the hypothalamus and the anterior pituitary is severed (e.g., there is damage to the pituitary stalk), secretion of all anterior pituitary hormones decreases, except prolactin, which increases. The secretion of prolactin increases because a chronic source of inhibition (PIF) has been removed.

TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone or thyrotropin
CRH = corticotropin-releasing hormone
ACTH = adrenocorticotropic hormone or corticotropin
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
FSH = follicle-stimulating hormone
GHRH = growth hormone–releasing hormone
GH = growth hormone
PIF = prolactin-inhibiting factor

Figure X-2-2. Control of the Anterior Pituitary

DISORDERS OF THE HYPOTHALAMIC–ANTERIOR PITUITARY

Hypopituitarism

- Can be inherited but more commonly acquired and may reflect the mass effects of tumors, inflammation, or vascular damage
- Large pituitary adenoma characteristic sequential loss of function: growth hormone and gonadotropin, followed by TSH then ACTH and finally prolactin.
- Isolated deficiency:

  Growth hormone: sporadic or familial

  Gonadotropins: Kallman syndrome – (tertiary) defective GnRH synthesis; ↓LH ↓FSH ↓sex steroids

  ACTH, TSH, and prolactin extremely rare deficiencies, usually a sign of panhypopituitarism
- Craniopharyngioma is the most common tumor affecting the hypothalamic–pituitary system in children (pituitary adenomas rare).
- Low trophic as well as low target hormones, e.g., ↓TSH ↓T4; ↓LH ↓Testosterone
- Stimulation tests: GnRH → LH, FSH; TRH→ TSH, prolactin; insulin infusion → GH, ACTH

Sheehan syndrome

The pituitary in pregnancy is enlarged and therefore more vulnerable to infarction. Sometimes when delivery is associated with severe blood loss, the ensuing shock causes arteriolar spasm in the pituitary with subsequent ischemic necrosis. Some degree of hypopituitarism has been reported in 32% of women with severe postpartum hemorrhage. Symptoms vary, depending on the extent and location of pituitary damage.

Pituitary Adenomas

- Most common cause of hypothalamic–pituitary dysfunction
- Microadenomas (< 1 cm. dia.): characterized by hormonal excess, no panhypopituitarism, treatable), e.g., ACTH (Cushing's disease)
- Macroadenomas (> 1 cm. dia): mass effect, larger tumors with suprasellar extension, associated with panhypopituitarism and visual loss
- Hypogonadism is the most common manifestation.
- Usually benign and can autonomously secrete hormone leading to hyperprolactinemia (60%), acromegaly (growth hormone 20%), and Cushing's disease (ACTH 10%).
- Prolactinomas associated with hypogonadism and galactorrhea
- MEN 1 association

Chapter Summary

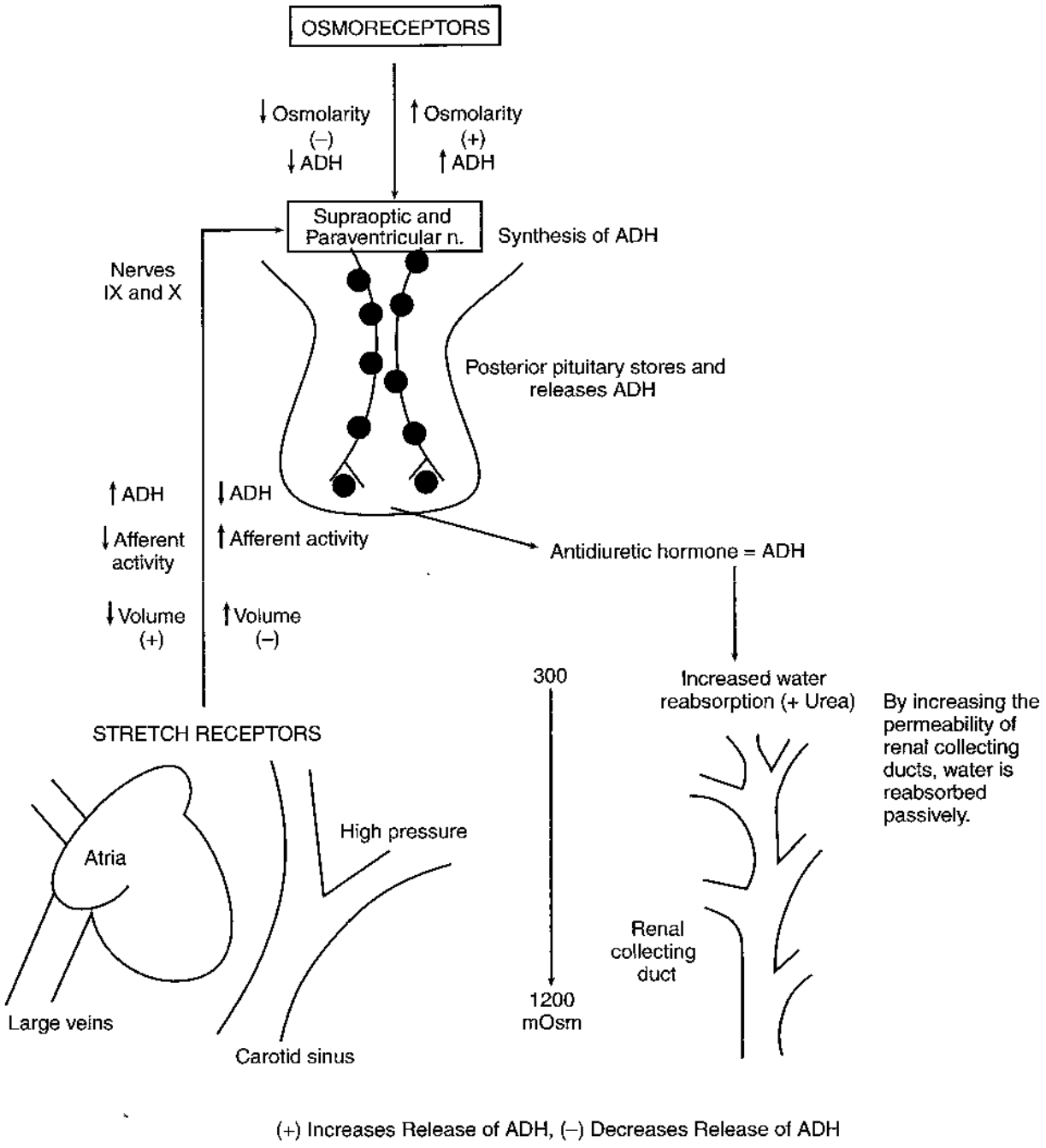
* Hypothalamic hormones affecting the pituitary are synthesized in the ventromedial, arcuate, and preoptic nuclei but are stored and released from the median eminence.
* Pulsatile system and the pulsatile release of GnRH prevents downregulation of gonadotroph receptors.
* Anterior pituitary hormones are regulated primarily by hypothalamic releasing hormones, except prolactin, which is mainly under the influence of PIF, an inhibiting hormone.
* Damage to the pituitary stalk causes a decrease in all anterior pituitary hormones except prolactin, which increases.
* Pituitary adenomas are the most common cause of anterior pituitary dysfunction.
* The mass effect causes sequential loss of GH and gonadotropin followed by TSH, ACTH, and finally prolactin.
* Prolactinomas are the most common tumor, and hypogonadism is the most common manifestation.

Posterior Pituitary

GENERAL FEATURES

- Made up of distal neuron terminals
- Secreted hormones; arginine vasopressin (ADH), oxytocin (see chapter 11)— both are peptide hormones.
- Cell bodies located in the supraoptic nucleus (mainly ADH synthesis) and paraventricular nucleus (mainly oxytocin synthesis) of the hypothalamus.
- ADH is a major controller of water excretion and ECF volume. ADH also controls osmolarity.
- The osmoreceptor neurons in the hypothalamus are extremely sensitive and are able to maintain ECF osmolarity within a very narrow range.
- There is a reseting of the osmostat downward in pregnancy, the menstrual cycle, and with volume depletion. In the latter case osmoregulation is secondary to volume regulation; a return of circulating volume will occur even as osmolarity decreases.
- Volume receptors are less sensitive than osmoreceptors and a change of 10–15% in volume is required to produce a measureable change in ADH.
- Cortisol and thyroid hormone restrain the release of ADH.

Figure X-3-1 illustrates the neural control mechanisms that regulate secretion of ADH by the posterior pituitary. The principal inputs are inhibition by baroreceptor and volume receptor unit and stimulation by osmoreceptors.



(+) Increases Release of ADH, (–) Decreases Release of ADH

Figure X-3-1. Neural Control Mechanism

Synthesis and Release of ADH

- ADH is synthesized in the hypothalamus, mainly in the supraoptic nucleus (SO), but also in the paraventricular nucleus (PVN); it is stored and released from the posterior pituitary.
- Osmoreceptors are neurons that respond to increased plasma osmolarity, principally plasma sodium concentration. They synapse with neurons of the SO and PVN and stimulate them to secrete ADH from the posterior pituitary. They also stimulate consumption of water through hypothalamic centers that regulate thirst.
- The SO and PVN also receive input from atrial and other volume receptors, as well as arterial baroreceptors. High blood volume or blood pressure tends to inhibit secretion of ADH.
- Secretion of ADH is most sensitive to plasma osmolarity; however, if blood volume decreases (such as hemorrhage) or cardiac output fails, high levels of ADH are secreted even if it causes abnormal plasma osmolarity.

Action of ADH

- The main target tissue is the renal collecting duct (V2 receptors).
- ADH increases the permeability of the duct to water by placing water channels in the luminal membrane.
- Water is reabsorbed passively, drawn across the membranes by the higher osmolarity of the interstitium.
- Urea can pass with the water, but electrolytes cannot.
- In severe hemorrhage, high levels of ADH via V1 receptors on vascular smooth muscle cause a vasoconstriction.

Regulation of ECF Volume and Osmolarity

Volume regulation

- Stimuli arising from stretch receptors act to chronically inhibit ADH secretion.
- Decreases in blood volume cause venous and arterial stretch receptors to send fewer signals to the CNS, decreasing chronic inhibition of ADH secretion.
- This mechanism is especially important for restoring ECF volume following a hemorrhage.

Osmoregulation

- An increase of only 1% in the osmolality of the ECF bathing the hypothalamic osmoreceptors will evoke an increased rate of ADH secretion.
- A similarly sized decrease in osmolality will decrease ADH secretion.
- In this manner, ECF osmolality is kept very close to 285 mOsm/L.

Effect of Alcohol and Weightlessness on ADH Secretion

Ingesting ethyl alcohol or being in a weightless environment suppresses ADH secretion. In weightlessness, there is a net shift of blood from the limbs to the abdomen and chest. This results in greater stretch of the volume receptors in the large veins and atria, thus suppressing ADH secretion.

ATRIAL NATRIURETIC PEPTIDE (ANP)

ANP is the hormone secreted by the heart. ANP is found throughout the heart but mainly in the right atrium. The stimuli that release ANP (two peptides are released) are:

- Stretch, an action independent of nervous involvement
- Increased salt intake

ANP increases sodium loss (natriuresis) and water loss by the kidney because of, in part, an increase in glomerular filtration rate due to:

- ANP-mediated dilation of the afferent arteriole
- ANP-mediated constriction of the efferent arteriole

ANP also increases sodium loss (natriuresis) and water loss (diuresis) by the kidney because of an inhibition of the reabsorption of sodium and water in the collecting duct.

The physiologic importance of ANP is not known because it has not been possible to identify or produce a specific deficiency state in humans. However, ANP secretion increases in weightlessness (submersion to the neck in water), while renin, aldosterone, and ADH secretion decrease. Thus, along with other hormones, it may play a role in normal regulation of the ECF osmolality and volume.

ANP tends to antagonize the effects of angiotensin II and ADH.

PATHOPHYSIOLOGIC CHANGES IN ADH SECRETION

Diabetes Insipidus

All the consequences can be explained on the basis of the lack of an effect of ADH on the renal collecting ducts.

Central diabetes insipidus

- Sufficient ADH is not available to affect the renal collecting ducts.
- Causes include familial, tumors (craniopharyngioma), autoimmune, trauma
- Pituitary trauma – transient diabetes insipidus
- Sectioning of pituitary stalk – triphasic response: diabetes insipidus, followed by SIADH, followed by a return of diabetes insipidus

Nephrogenic diabetes insipidus

- Due to inability of the kidneys to respond to ADH
- Causes include familial, acquired, drugs (lithium)

Table X-3-1. Differential Diagnosis Following Water Deprivation

	Plasma Osm	Urine Osm	Plasma ADH	Urine Osm Post Desmopressin
Normal	297	814	↑	815
Central DI*	342	102	↓	622
Nephrogenic	327	106	↑	118

*Patients with partial central DI will concentrate their urine somewhat but will achieve an additional boost following desmopressin.

Syndrome of Inappropriate ADH Secretion (SIADH)

Excessive secretion of ADH causes an inappropriate increased reabsorption of water in the renal collecting duct.

Causes

- Ectopic production of ADH (small cell carcinoma of the lung)
- Drug induced
- Lesions in the pathway of the baroreceptor system

Pathophysiology

- Increased water retention, hyponatremia, but clinically euvolumic
- Volume expansion increases ANP, decreases renin creating a natriuresis, which contributes to the hyponatremia
- Inappropriate concentration of urine, usually greater than plasma osmolarity
- A small, constant secretion of ADH by a tumor may have a minimal effect on the ability to form dilute urine but has a major effect on the ability to excrete a large water load.

Treatment

- Fluid restriction but not salt restriction

Summary of Changes

Table X-3-2. The Effects of Diabetes Insipidus, Dehydration, SIADH, and Primary Polydipsia

	Diabetes Insipidus	Dehydration	SIADH	Primary Polydipsia
1. Permeability of collecting ducts to H_2O	↓	↑	↑	↓
2. Urine flow	↑	↓	↓	↑
3. Urine osmolarity	↓	↑	↑	↓
4. ECF volume	↓	↓	↑	↑
5. ECF osmolarity* (Na concentration)	↑	↑	↓	↓
6. ICF volume	↓	↓	↑	↑
7. ICF osmolarity	↑	↑	↓	↓

*Overt physical and laboratory signs of dehydration do not necessarily develop unless there is a defect in thirst stimulation.

HYPONATREMIA

General Features

- One of the most common disorders of fluid and electrolyte balance in hospitalized patients
- Is usually equivalent to a hypo-osmolar state (exception hyperglycemia)

- Involves both solute depletion and water retention but water retention is usually the more important factor
- Solute depletion can occur from any significant loss of ECF fluid. The hyponatremia is the result of replacement by more hypotonic fluids.
- When it develops rapidly (< 48 hours) and is severe (Na < 120 mEq/L), patient is at risk for cerebral edema and herniation of brain stem. Symptoms include edema, seizures, and respiratory arrest. Often treated aggressively with hypertonic saline (3%) and diuretics.
- When it develops more slowly, it appears to be well-tolerated and patient is asymptomatic. Aggressive treatment may result in "central pontine myelinosis." General recommendation is to slowly raise Na concentration over a period of days.

Subgroups

Type I: Hypervolemia. Caused by marked reduction in water excretion and/or increased rate of water ingestion. Would include congestive heart failure and cirrhosis

Type II: Hypovolemia. Indicates solute depletion. Would include mineralocorticoid deficiency, diuretic abuse, renal disease, diarrhea, and hemorrhage

Type III: Clinical euvolemia. Would include SIADH. A clinically equivalent presentation may occur in glucocorticoid deficiency.

Chapter Summary

* ADH is synthesized in the hypothalamus but is stored and released from the posterior pituitary.
* The major action of ADH is the passive reabsorption of water and urea, but not electrolytes, in the renal collecting duct.
* Osmoreceptors are very sensitive and normally maintain osmolarity in a very narrow range.
* Reduced input from the low-pressure stretch receptors is a strong stimulus for the release of ADH.
* ANP, found mainly in the tissue of the right atrium, is released in response to stretch. The major action of ANP is diuresis and natriuresis.
* In diabetes insipidus, central form has low plasma ADH, nephrogenic form has high plasma ADH.
* Easily separated by measuring plasma ADH or injection of desmopressin
* Differential diagnosis following water deprivation
* SIADH: Inappropriate elevated secretion of ADH. Characterized by euvolemia but hyponatremia.
* Acute hyponatremia is life threatening if severe. Treated aggressively.
* Chronic hyponatremia is usually well-tolerated. Aggressive treatment is associated with central pontine myelinosis.

Adrenal Cortex

LAYERS OF THE ADRENAL CORTEX AND THEIR ROLE IN HORMONE FORMATION

General Features

Figure X-4-1 summarizes each adrenal region.

- ACTH controls the release of both cortisol and adrenal androgens.
- Although a separate hormone that affects adrenal androgens has been proposed, it has not been characterized.
- The main factor regulating aldosterone secretion is angiotensin II.

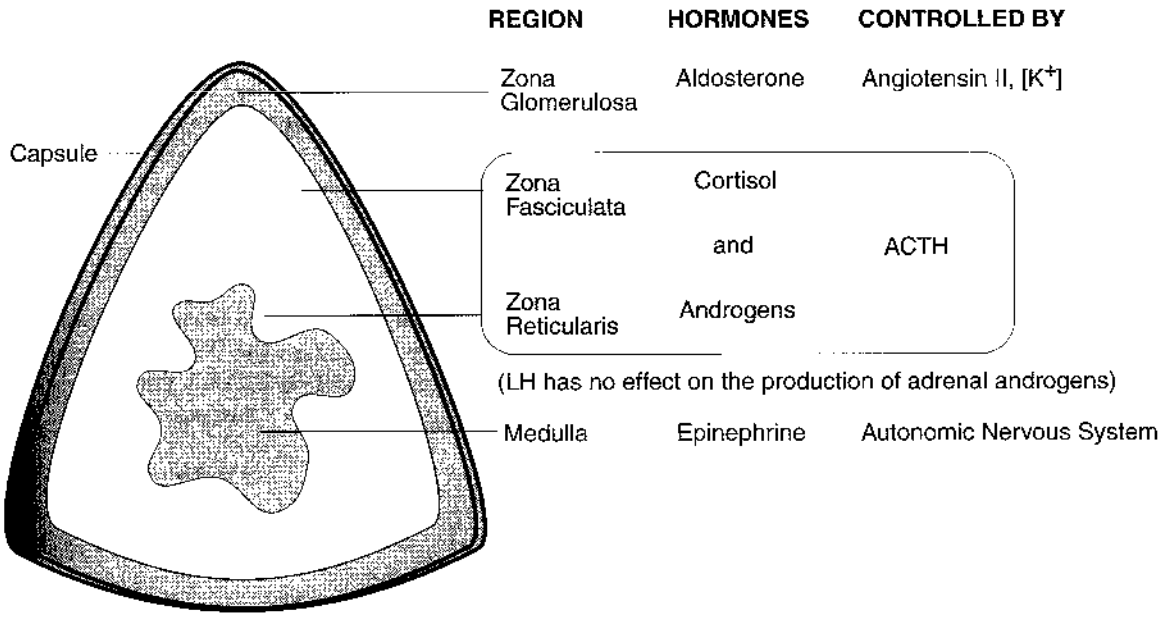


Figure X-4-1. Adrenal Cortex Regions

Consequences of the Loss of Regional Adrenal Function

Zona glomerulosa: The absence of the mineralocorticoid, aldosterone, results in:

- Loss of Na^+
- Decreased volume of the ECF
- Low blood pressure
- Circulatory shock
- Death (mineralocorticoid is generally required for survival)

Zona fasciculata, zona reticularis: The **absence of the glucocorticoid, cortisol,** contributes to:

- Circulatory failure, because without cortisol, catecholamines do not exert their normal vasoconstrictive action.
- An inability to readily mobilize energy sources (glucose and free fatty acids) from glycogen or fat. Under normal living conditions, this is not life-threatening; however, under stressful situations, severe problems can arise. For example, fasting can result in fatal hypoglycemia.

Medulla: The **absence of the catecholamine, epinephrine** (the major hormone of the adrenal medulla):

- Decreases the capacity of the individual to mobilize glycogen or fat during exercise or cold exposure; however, the adrenal medulla is not essential for survival.

Note: If problems develop with anterior pituitary secretion, glucocorticoid secretion may be affected, but the mineralocorticoid system remains intact.

BIOSYNTHETIC PATHWAYS OF STEROID HORMONE SYNTHESIS

The Synthetic Pathways

Overview

Figure X-4-2 shows a composite of the synthetic pathways in all steroid hormone-producing tissues. A single tissue has only the pathways necessary to produce the hormones normally secreted by that particular tissue. For example, the zona glomerulosa has only the pathways of the first column because the main output of the zona glomerulosa is aldosterone.

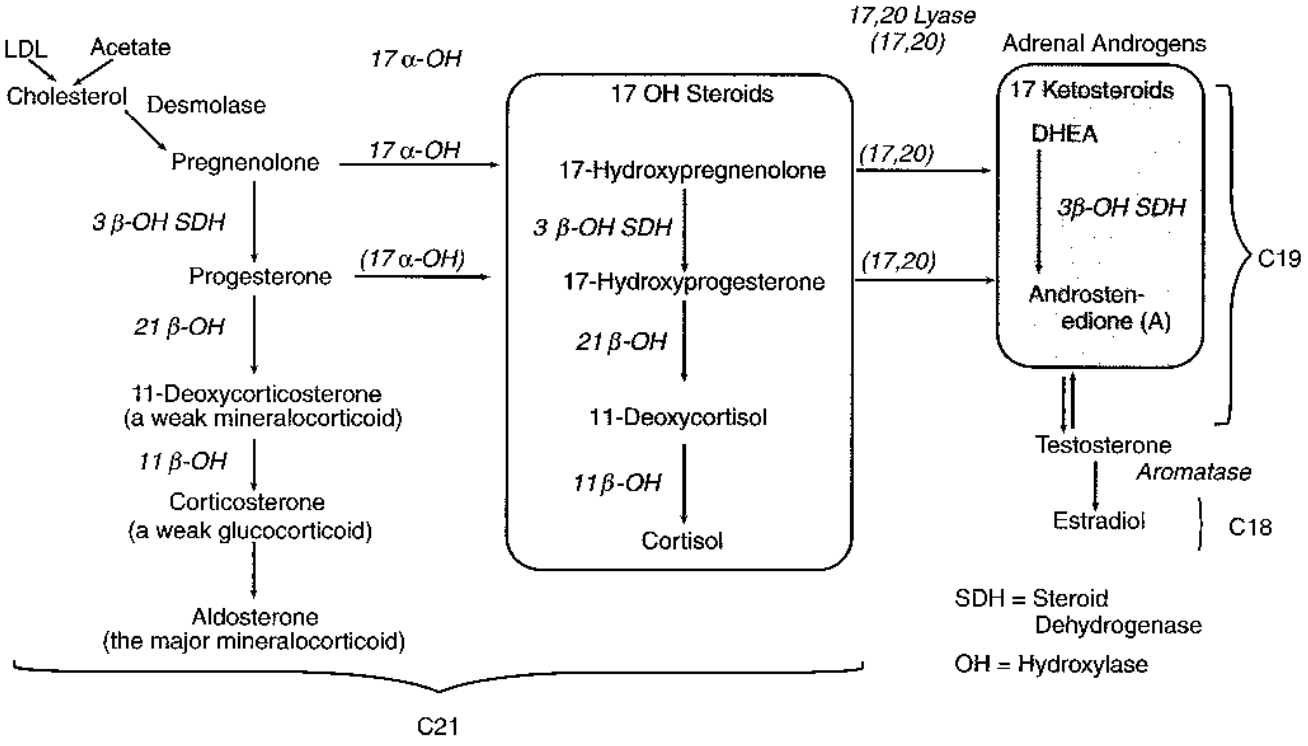


Figure X-4-2. Pathways of Adrenal Steroid Synthesis

C21 steroids (21 carbon atoms)

C21 steroids with an OH at position 17 are called 17-hydroxysteroids. The only 17 OH steroid with hormonal activity is cortisol.

The lipid-soluble 17 OH steroids are metabolized to water-soluble compounds before they are filtered and excreted in the urine. The pathway for cortisol is shown in Figure X-4-3.

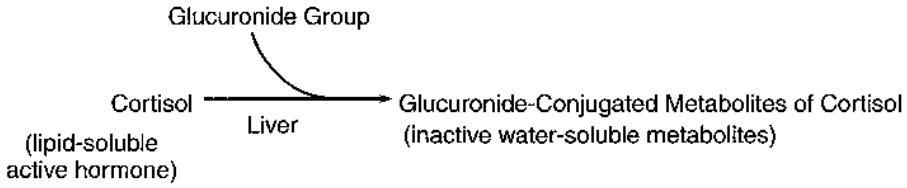


Figure X-4-3. Metabolism of Cortisol

Urinary 17 OH steroids have in the past been measured as an index of cortisol secretion. This has been replaced by the measurement of the 24-hour urine-free cortisol.

C19 steroids (19 carbon atoms)

Adrenal Androgens

- Have a keto group at position 17 and therefore are called 17-ketosteroids.
- Are conjugated with sulfate in the adrenal cortex, making them water soluble. As water-soluble metabolites, they circulate in the bloodstream, are filtered by the kidney, and are excreted in the urine. The sulfated form is not produced in the gonads and is thus considered an index of androgen production by the adrenals.
- The major secreted form is dehydroepiandrosterone (DHEA).
- DHEA, DHEA sulfate, and androstenedione have very low androgenic activity. They function primarily as precursors for the peripheral conversion to the more potent testosterone and dihydrotestosterone (men and women).
- In adult males, excessive production of adrenal androgens has no clinical consequences. In prepubertal males it causes premature penile enlargement and early development of secondary sexual characteristics. In women excessive adrenal androgens cause hirsutism and virilization.

Testosterone

- Produced mainly by the Leydig cells of testes
- The active hormone is lipid-soluble and not a 17-ketosteroid.
- When metabolized, it is converted to a 17-ketosteroid and conjugated to become water soluble. In this form, it is filtered and excreted by the kidney.

Urinary Excretion

- Urinary 17-ketosteroids are an index of all androgens, adrenal and testicular.
- In females and prepubertal males, urinary 17-ketosteroids are an index of adrenal androgen secretion.
- In adult males (postpuberty), urinary 17-ketosteroids are 2/3 adrenal and 1/3 testicular, and thus mainly an index of adrenal secretion.

C18 steroids—estrogens (e.g., estradiol)

- Aromatase converts androgen into estrogen.

Regional Synthesis

Conversion of cholesterol to pregnenolone

The starting point in the synthesis of all steroid hormones is the conversion of cholesterol to pregnenolone.

The enzyme catalyzing this conversion is desmolase. This is a rate-controlling step in all steroid hormone synthesis.

Synthesis in the zona glomerulosa

Figure X-4-4 represents the pathways present in the zona glomerulosa. Angiotensin II is the main stimulus to the zona glomerulosa, which produces aldosterone, the major mineralocorticoid.

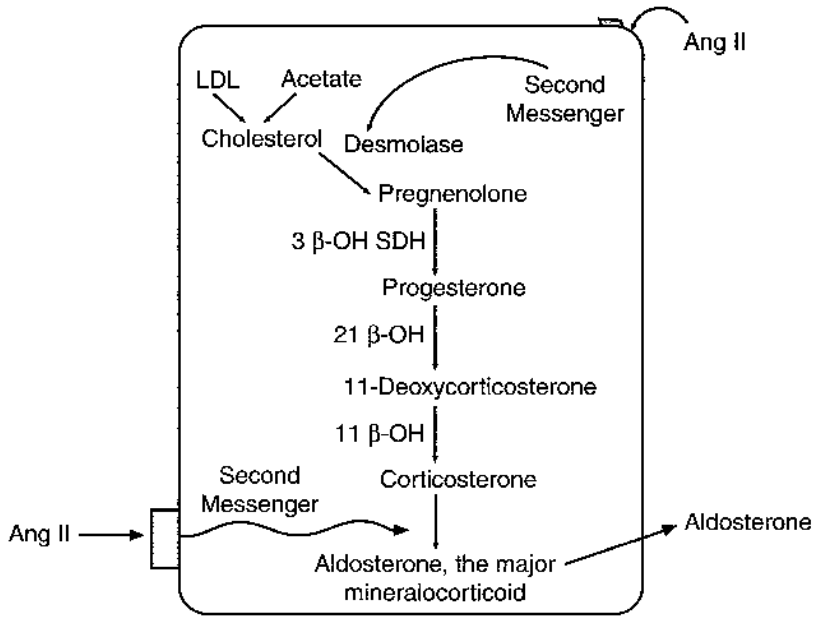


Figure X-4-4. Pathway to Aldosterone Synthesis

Synthesis in the zona fasciculata and the zona reticularis

Figure X-4-5 represents the control of steroid hormone synthesis in the zona fasciculata and the zona reticularis.

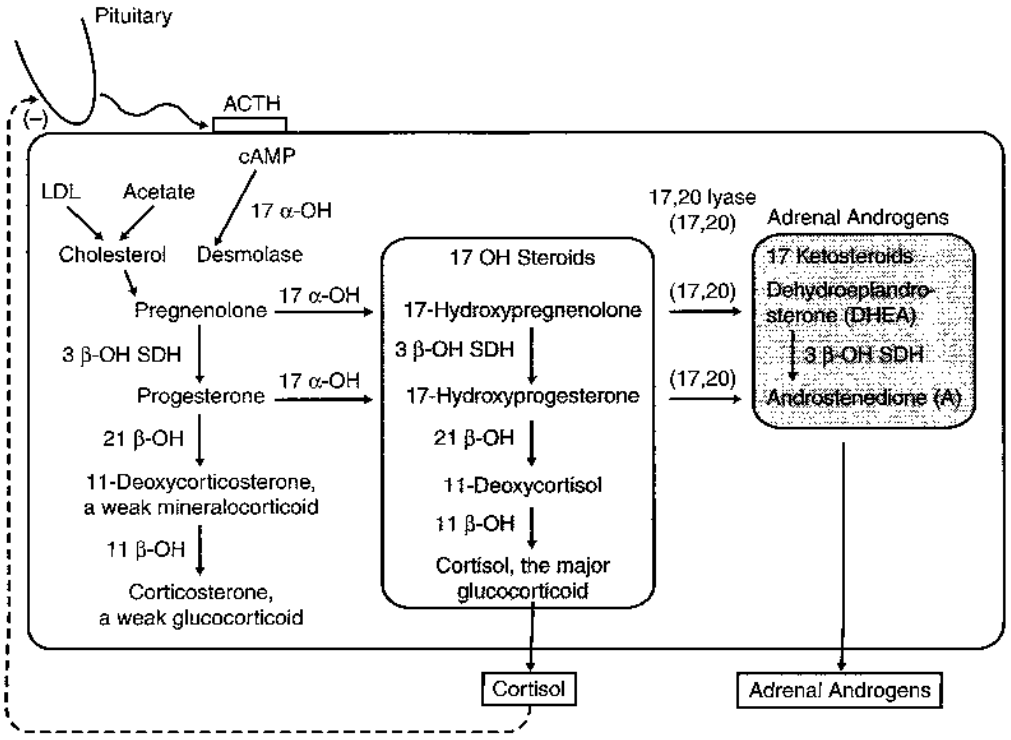


Figure X-4-5. Pathway to Cortisol Synthesis

Normal hormonal output of the zona fasciculata and zona reticularis consists of the following:

- 11-Deoxycorticosterone: Under normal conditions, this weak mineralocorticoid is not important. Almost all mineralocorticoid activity is due to aldosterone.
- Corticosterone: Also not important under normal conditions. Almost all glucocorticoid activity is due to cortisol.
- Adrenal androgens: These weak water-soluble androgens represent a significant secretion; however, they produce masculinizing characteristics only in women and prepubertal males when secretion is excessive.
- Cortisol: Main glucocorticoid secreted by the adrenal cortex, responsible for most of the hypothalamic and anterior pituitary negative feedback control of ACTH secretion.

PHYSIOLOGIC ACTIONS OF GLUCOCORTICOIDS

Stress (Includes States Such as Trauma, Exposure to Cold, Illness, Starvation, and Exercise)

The capacity to withstand stress is dependent on adequate secretion of the glucocorticoids.

Stress hormones usually act to mobilize energy stores. The stress hormones are:

- Growth hormone: mobilizes fatty acids by increasing lipolysis in adipose tissue
- Glucagon: mobilizes glucose by increasing liver glycogenolysis
- Cortisol (does not increase in starvation): mobilizes fat, protein, carbohydrate (see below)
- Epinephrine, in some forms of stress such as exercise: mobilizes glucose via glycogenolysis and fat via lipolysis

All stress hormones raise plasma glucose. Severe hypoglycemia is a crisis and causes a rapid increase in all stress hormones. By definition, because these hormones raise plasma glucose, they are referred to as counterregulatory hormones (opposite to insulin). One of the most sensitive stimulation tests for a stress hormone is an insulin-induced hypoglycemia. While it is often the most sensitive test, it is also a dangerous test.

A deficiency in a stress hormone often causes episodes of hypoglycemia

Insulin tends to decrease in stress because it mainly promotes the storage of the products of digestion.

Metabolic Actions of Cortisol

Cortisol promotes the mobilization of energy stores, specifically:

- Protein: Cortisol promotes degradation and increased delivery of amino acids.
- Lipids: Cortisol promotes lipolysis and increased delivery of free fatty acids and glycerol.
- Carbohydrate: Cortisol raises blood glucose, making more glucose available for nervous tissue. Two mechanisms are involved:
  - Cortisol inhibits glucose uptake in most tissues (muscle, lymphoid, and fat).
  - Cortisol increases hepatic output of glucose via gluconeogenesis from amino acids in particular (not from liver glycogenolysis).

Permissive Actions of Cortisol

Cortisol enhances the capacity of glucagon and catecholamines, hence the adjective *permissive* aptly describes many of the actions of cortisol.

Glucagon

Promotes glycogenolysis in the liver (some lipolysis from adipocytes as well). Without cortisol, fasting hypoglycemia rapidly develops.

Catecholamines

Promote glycogenolysis and lipolysis in liver and muscle. Promote vasoconstriction and bronchodilation. Without cortisol, blood pressure decreases.

CONTROL OF ADRENOCORTICOTROPIN (ACTH) AND CORTISOL SECRETION

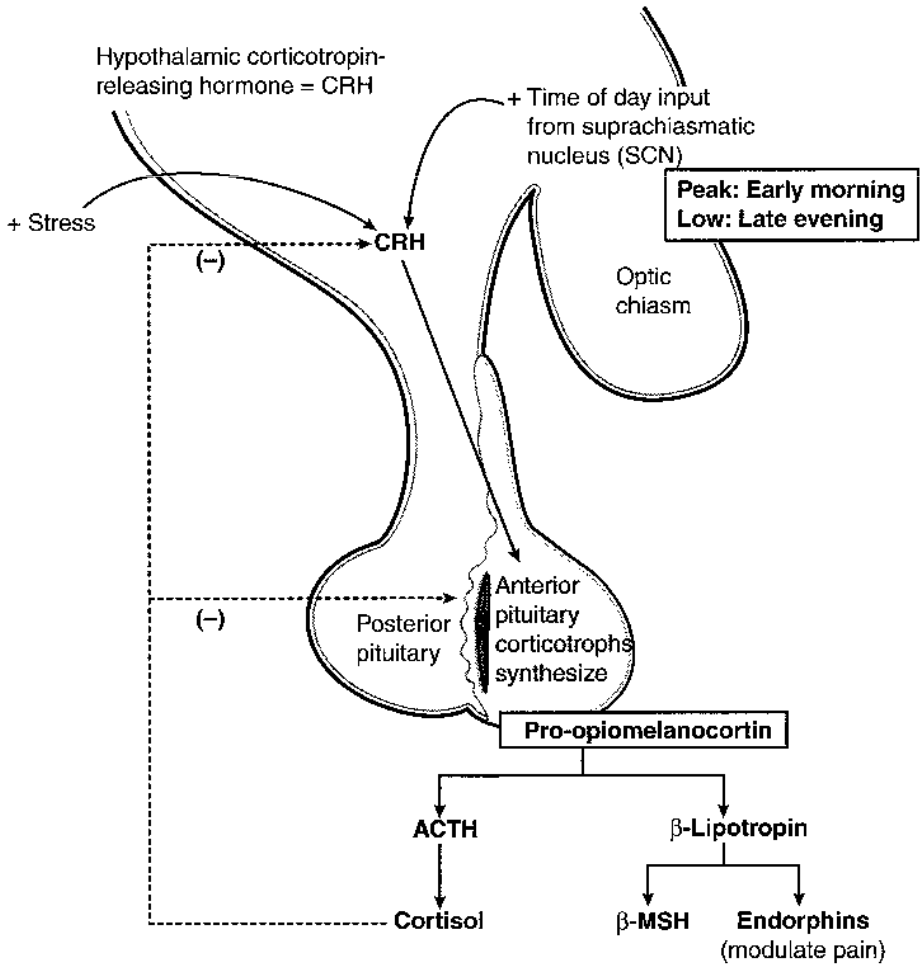


Figure X-4-6. Control of ACTH and Cortisol

Role of the Specific Modulators

Corticotropin-Releasing Hormone (CRH)

Secretion of CRH increases in response to stress and in the early morning:

- Peak cortisol secretion occurs early in the morning between the 6th and 8th hours of sleep. Secretion then declines slowly during the day and reaches a low point late in the evening.

ACTH

Stimulates the secretion of cortisol (and adrenal androgens) of adrenal cortex. Cortisol suppresses the release of ACTH by acting on the hypothalamus and anterior pituitary.

Excessive secretion of ACTH (e.g., Addison's disease) causes darkening of the skin. This is due to the melanocyte-stimulating hormone (α-MSH) sequence within the ACTH molecule, and the β-MSH activity of β-lipoprotein.

β-Lipotropin

- Role not well understood
- Precursor to β-MSH and endorphins. Endorphins may modulate the perception of pain.

PHYSIOLOGIC ACTIONS OF ALDOSTERONE

General Features

1. The primary target tissue for aldosterone is the kidney, where its most important action is to increase Na^+ reabsorption by the principal cells of the kidney's collecting ducts. Because water is reabsorbed along with the Na^+, aldosterone can be considered to control the amount of Na^+ rather than the concentration of Na^+ in the ECF.
2. Aldosterone also promotes the secretion of H^+ by the intercalated cells of the collecting duct, and K^+ secretion by the principal cells.
3. The Na^+-conserving action of aldosterone is also seen in salivary ducts, sweat glands, and the distal colon.
4. Figure X-4-7 shows the overall effects of aldosterone. This is a generalized representation of the effect of aldosterone on the renal distal tubule/collecting duct region.

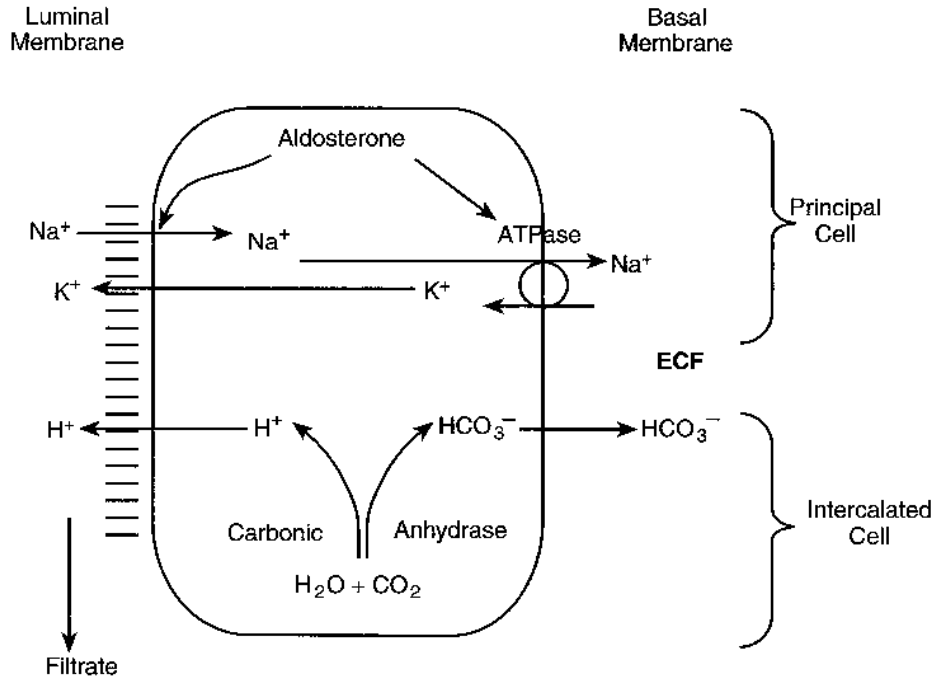


Figure X-4-7. Late Distal Tubule and Collecting Duct

Specific Actions of Aldosterone

1. Aldosterone promotes the activity of Na/K-ATPase–dependent pump that moves Na^+ into the renal ECF in exchange for K^+. Because the lumen is somewhat impermeable to NaCl, aldosterone also increases the number of Na^+ channels in the luminal membrane, thus increasing the passive movement of Na^+ from the filtrate into the cell. The net effect is to remove Na^+ from the filtrate and pump it into the ECF. Generally, water is retained with the sodium, and little change is seen in sodium concentration of the extracellular fluid.
2. A consequence of the above action is that the tubule lumen becomes more negatively charged than the ECF. This negative charge attracts K^+. Thus, aldosterone facilitates K^+ secretion into the distal tubule/collecting duct. Aldosterone also increases secretion of potassium because of its stimulation of K^+ transport into the tubular cells; this raises intracellular K^+ level, which promotes leakage into the tubular fluid. K^+ preferentially leaks into the tubular fluid because aldosterone also increases permeability of the luminal surface to potassium.
3. The negative charge also attracts H^+ and therefore facilitates H^+ secretion into the distal tubule/collecting duct and its loss in the urine.

Whenever a H^+ is secreted, a HCO_3^- moves into the ECF. This represents new HCO_3^- added to body stores. Therefore, aldosterone tends to promote metabolic alkalosis.

Table X-4-1. Actions of Aldosterone

	Renal	Effects
Na^+	reabsorption	↑ total body Na^+
K^+	secretion	↓ plasma $[K^+]$
H^+	secretion	metabolic alkalosis
HCO_3^-	production	metabolic alkalosis
H_2O	reabsorption	volume expansion

CONTROL OF ALDOSTERONE SECRETION

Controlling Factors

ACTH is of minor importance in the control of aldosterone secretion. It can stimulate aldosterone secretion, but this is a transient effect. Physiologically, aldosterone is largely under the control of the renin-angiotensin system.

Sensory Input—the Juxtaglomerular Apparatus

The main sensory cells are the juxtaglomerular cells. They are modified smooth-muscle cells which surround and directly monitor the pressure in the afferent arteriole. This signal in many cases is in response to a reduction in circulating fluid volume.

These cells are also innervated and stimulated by sympathetic neurons via norepinephrine and beta receptors. Thus the release of renin induced by hypovolemia is enhanced by increased sympathetic neural activity.

Additional sensory input is from the macula densa cells of the distal tubule. They perceive sodium delivery to the distal nephron and communicate with the juxtaglomerular cells.

The juxtaglomerular apparatus is represented in Figure X-4-8.

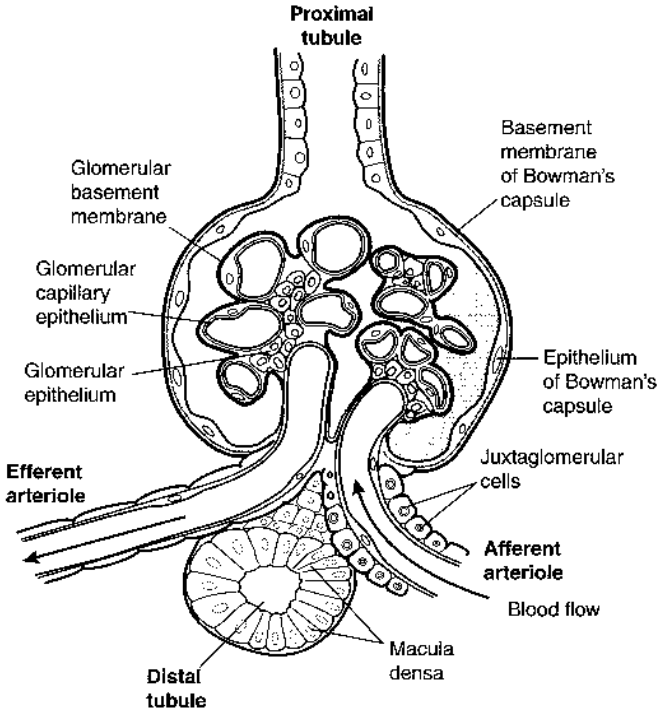


Figure X-4-8. Renal Corpuscle and Juxtaglomerular Apparatus

Long-term Regulation of Blood Pressure and Cardiac Output by the Renin-Angiotensin-Aldosterone System

Long-term regulation of blood pressure and cardiac output is accomplished by the renin-angiotensin-aldosterone system.

Blood pressure is monitored by the juxtaglomerular apparatus. When renal perfusion pressure decreases, secretion of renin increases; conversely, when pressure increases, renin secretion is suppressed. Renin is an enzyme that converts a circulating protein produced in the liver, **angiotensinogen**, also called **renin substrate**, into **angiotensin I**. Angiotensin converting enzyme (ACE), found mainly in endothelial cells of pulmonary vessels, converts angiotensin I into **angiotensin II**. Angiotensin II has potent effects to stimulate secretion of aldosterone and to cause arteriolar vasoconstriction. It also directly stimulates reabsorption of sodium in the proximal tubule.

$$MAP = CO \times TPR$$

This system regulates both resistance, via vasoconstriction, and cardiac output, via preload. Since aldosterone also causes increased renal excretion of potassium, it affects plasma potassium concentration. Plasma potassium strongly stimulates secretion of aldosterone, so this constitutes a negative-feedback control system for plasma potassium concentration.

Volume-depleted states tend to produce metabolic alkalosis, in part because aldosterone increases to compensate for the volume loss; the aldosterone increase stimulates excretion of acid and addition of bicarbonate to the plasma.

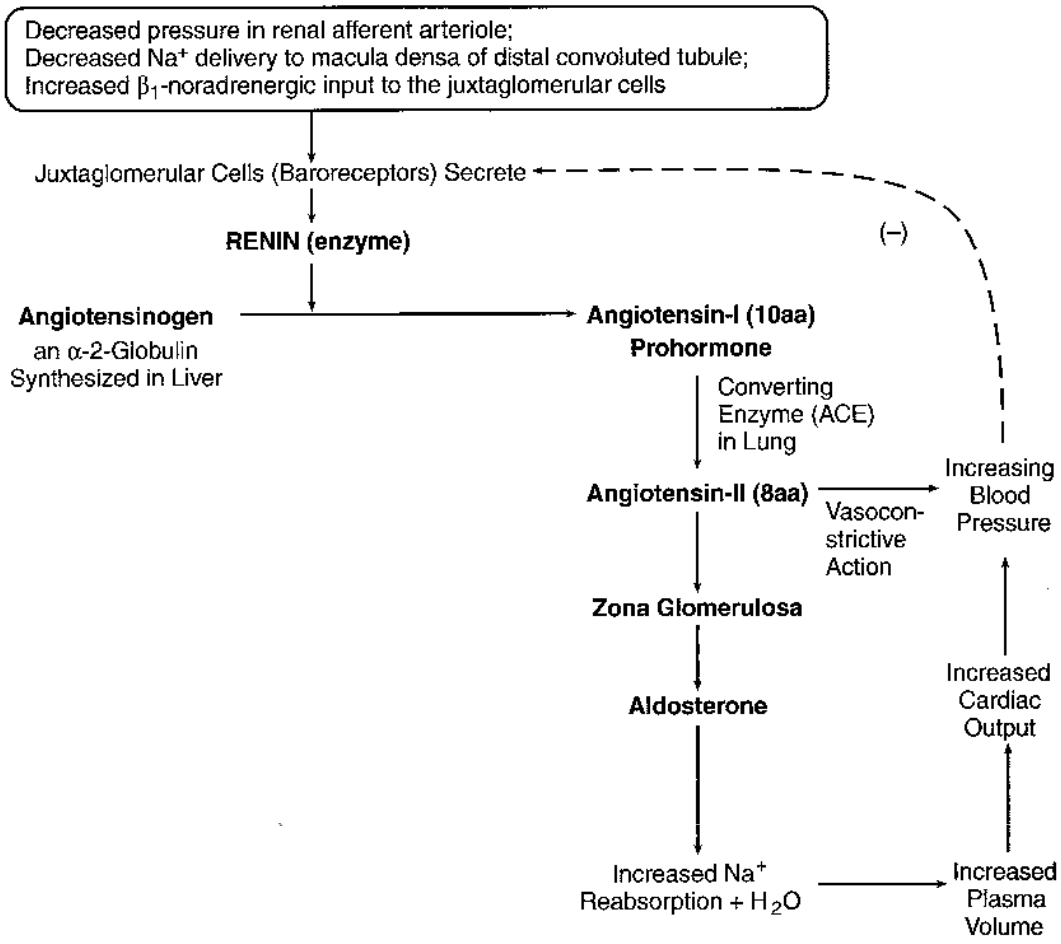


Figure X-4-9. Feedback control of Blood Pressure by Renin-Angiotensin-Aldosterone System

Any of the three stimuli listed at the top of the figure will produce an increase in the secretion of renin and circulating angiotensin II. Angiotensin II raises blood pressure by two independent actions:

- The direct vasoconstrictive effects of angiotensin II increase total peripheral resistance.
- It stimulates the adrenal cortex to secrete aldosterone, resulting in increased reabsorption of Na^+.

As Na^+ reabsorption is increased, so is water. This increases the volume of the ECF, the plasma, and the blood, thus raising cardiac output and blood pressure.

An increase in blood pressure will suppress the renin-angiotensin-aldosterone system. This decrease in angiotensin II will decrease total peripheral resistance. Reduced activity of aldosterone will cause a urinary loss of sodium and water, lowering cardiac output.

Potassium Effect

In addition to the preceding system, elevated plasma K^+ (hyperkalemia) increases the secretion of aldosterone by directly stimulating the zona glomerulosa.

A small increase in the plasma potassium level can cause a several-fold increase in aldosterone secretion.

Physiologic Changes in Aldosterone Secretion

Increased aldosterone secretion

Increased aldosterone secretion is any condition that decreases pressure in the renal artery (e.g., hemorrhage, prolonged sweating) will activate the renin-angiotensin system, increase aldosterone secretion, and increase sympathetic stimulation to return blood pressure toward normal.

Decreased aldosterone secretion

Decreased aldosterone secretion is any condition that increases blood pressure in the renal artery.

This includes weightlessness, because blood no longer pools in the extremities when the individual is standing or sitting. A large portion of the redistributed blood ends up in the atria and large veins of the chest and abdomen. The increased distention of these vessels stimulates baroreceptors located there. Signals from these baroreceptors reach the vasomotor center, where they inhibit sympathetic output, including sympathetic signals that normally promote renin secretion by the juxtaglomerular cells. As a result, less renin, angiotensin II, and aldosterone are secreted, causing individuals to lose Na^+ and ECF volume.

GLUCOCORTICOID DISORDERS

Definitions

Cushing's syndrome: hypercortisolism regardless of origin, including chronic glucocorticoid therapy

Cushing's disease: hypercortisolism due to an adenoma of the anterior pituitary (microadenoma)

Suppression Tests

Low-dose dexamethazone

- For the presence of Cushing's syndrome regardless of the cause
- Normal; cortisol decreases
- Hypercortisolism; cortisol not suppressed

High-dose dexamethazone

- To differentiate Cushing's disease from ectopic ACTH secretion and adrenal tumors
- Cushing's disease; cortisol decreases
- Ectopic ACTH, adrenal tumor; cortisol not suppressed

Stimulation Tests

Rapid ACTH stimulation test

- To diagnose both primary and secondary hypocortisolism (atrophied adrenal nonresponsive)
- Normal; cortisol increases
- Hypocortisolism; cortisol no change

Metyrapone testing

- Mainly to access pituitary-adrenal reserve
- Inhibits 11 beta hydroxylase, thereby decreases cortisol
- Normal; ACTH increases, 11-deoxycortisol increases
- Alternative test is insulin-induced hypoglycemia

Hypercortisolism

Primary hypercortisolism

- ACTH independent
- Cortisol elevated, ACTH depressed
- Most are benign adrenocorticol adenomas
- Adrenal adenoma usually unilateral and secretes only cortisol; decreased adrenal androgen and deoxycorticosterone (hirsutism absent)
- Presence of androgen or mineralocorticoid excess suggests a carcinoma.

Secondary hypercortisolism

- ACTH dependent
- Hypersecretion of ACTH results in bilateral hyperplasia of the adrenal zona fasciculata and reticularis
- Elevated ACTH, cortisol, adrenal androgen, deoxycorticosterone
- Two main subcategories:
  - Cushing's disease:

    Cause is a pituitary adenoma usually a microadenoma (< 1 cm dia.)

    Most common pathological cause of Cushing's syndrome

    Increased ACTH not sufficient to cause hyperpigmentation

    Dexamethazone suppressible
  - Ectopic ACTH syndrome:

    Most frequently in patients with small cell carcinoma of the lung

    Greater secretion of ACTH than in Cushing's disease and hyperpigmentation often present

    Ectopic site nonsupressible with dexamethazone

    Typical features of Cushing's syndrome often absent due to malignancy

Differential diagnosis

- Hypercortisolism established by lack of cortisol suppression to low-dose dexamethazone and/or elevated 24-hour urine free cortisol
- Decreased plasma ACTH in primary, increased ACTH in secondary
- High-dose dexamethazone; ACTH suppressed = Cushing's disease; ACTH not suppressed = ectopic ACTH syndrome

Characteristics of Cushing's Syndrome

- Obesity, classically central affecting mainly the face, neck, trunk, and abdomen: "moon facies" and "buffalo hump"
- Protein depletion as a result of excessive protein catabolism
- Inhibition of inflammatory response and poor wound healing
- Hyperglycemia leads to hyperinsulinemia and insulin resistance.
- Hyperlipidemia
- Bone dissolution and osteoporosis
- Thinning of the skin with wide purple striae located around abdomen and hips
- Increased adrenal androgens, when present in women, can result in acne, mild hirsutism, and amenorrhea. In men, decreased libido and impotence
- Mineralocorticoid effects of the high level of glucocorticoid and deoxycorticosteroid lead to salt and water retention (hypertension), potassium depletion, and a hypokalemic alkalosis.
- Increased thirst and polyuria
- Anxiety, depression, and other emotional disorders may be present.

Hypocortisolism

Primary Hypocortisolism (in primary adrenal insufficiency, Addison's disease)

Cortisol deficiency leads to weakness, fatigue, anorexia, hypotension, hyponatremia, hypoglycemia. Increases in ACTH result in hyperpigmentation of skin and mucous membranes.

Aldosterone deficiency leads to sodium wasting and hyponatremia, potassium retention and hyperkalemia, dehydration, hypotension, and acidosis

- Autoimmune origin with slow onset in about 80% of cases
- Loss of 90% of both adrenals required before obvious clinical manifestations
- With gradual adrenal destruction, basal secretion is normal but secretion does not respond to stress, which may initiate an adrenal crisis.
- Bilateral hemorrhage as the origin results in an adrenal crisis. Hyperpigmentation, hyponatremia, and hyperkalemia usually absent
- Dehydration leading to hypotension with postural accentuation
- Abnormalities in GI function
- Loss of axillary and pubic hair in women due to loss of androgens, amenorrhea
- Insufficient glucocorticoids lead to hypoglycemia and an inability of the kidney to excrete a water load
- Severe hypoglycemia in children but rare in adults

Secondary hypocortisolism

- Most commonly due to sudden withdrawal of exogenous glucocorticoid therapy
- Pituitary or hypothalamic tumors most common natural origin of ACTH deficiency
- In the early stages baseline hormone values are normal but ACTH reserve compromised and stress response subnormal (glucocorticoids administered presurgery)
- May be associated with the loss of other anterior pituitary hormones (panhypopituitarism) or adenomas secreting prolactin or growth hormone
- Atrophy of the zona fasciculata and zona reticularis
- Zona glomerulosa and aldosterone normal; no manifestations of mineralocorticoid deficiency

- Consequences as stated for cortisol deficiency
- Severe hypoglycemia and severe hypotension unusual
- Hyponatremia due to water retention

Differential diagnosis

- Rapid ACTH stimulation test: initial procedure in the assessment of adrenal insufficiency, both primary and secondary. Normal: ↑ cortisol; hypocortisolism: no ↑ cortisol
- Normal responsiveness of ACTH test does not exclude decreased pituitary reserve and decreased response to stress (metyrapone; insulin infusion)
- In same sample, a normal aldosterone would be evidence of a secondary problem
- Definitive test for primary vs. secondary is ACTH: ↑primary hypocortisolism (Addison's); ↓ secondary hypocortisolism

Summary

Table X-4-2. Primary and Secondary Disorders of Cortisol Secretion

Disorder	Plasma Cortisol	Plasma ACTH	Hyperpigmentation
Primary hypercortisolism	↑	↓	no
Secondary hypercortisolism			
A. Cushing's disease	↑	normal or ↑	no
B. Ectopic ACTH	↑	↑	yes (maybe)
Primary hypocortisolism	↓	↑	yes
Secondary hypocortisolism	↓	↓	no

MINERALOCORTICOID DISORDERS

Hyperaldosteronism with Hypertension

Primary hyperaldosteronism (Conn's syndrome)

- Most common cause is a small unilateral adenoma, which may occur on either side.
- Remainder mostly bilateral adrenal hyperplasia (idiopathic hyperaldosteronism)
- Rarely due to adrenal carcinoma
- Increased whole body sodium, fluid, and circulating blood volume
- Hypernatremia is infrequent.
- Increased peripheral vasoconstriction and TPR
- Blood pressure from borderline to severe hypertension
- Edema rare (sodium escape*)
- Modest left ventricular hypertrophy
- Potassium depletion and hypokalemia create symptoms of weakness and fatigue.

*A major increase in sodium and water retention is prevented by "sodium escape" in primary hyperaldosteronism. Although the mechanism is not well understood, evidence exists that atrial natriuretic factor plays a role.

- Detection of hypertension with hypokalemia often the initial clue for Conn's syndrome
- Increased hydrogen ion excretion and new bicarbonate create metabolic alkalosis.
- A positive Chvostek's or Trousseau's sign suggestive of alkalosis
- Cortisol is normal.
- Suppression of renin a major feature

Secondary hyperaldosteronism refers to a state in which there is an appropriate increase in aldosterone in response to activation of the renin-angiotensin system.

Secondary hyperaldosteronism with hypertension

- In most cases a primary over-secretion of renin secondary to a decrease in renal blood flow and/or pressure
- Renal arterial stenosis, narrowing via atherosclerosis, fibromuscular hyperplasia.
- Renin-secreting tumor rare
- Modest to highly elevated renin
- Modest to highly elevated aldosterone
- Hypokalemia and metabolic alkalosis

Differential diagnosis

- Hypokalemia in a hypertensive patient not taking diuretics
- Hyposecretion of renin with elevated aldosterone that fails to respond to a volume contraction – Conn's syndrome
- Hypersecretion of renin with elevated aldosterone – renal vascular

Hyperaldosteronism with Hypotension

Secondary hyperaldosteronism with hypotension

Sequestration of blood on the venous side of the systemic circulation is a common cause of secondary hyperaldosteronism. This results in decreased cardiac output and thus decreased blood flow and pressure in the renal artery. The following conditions produce secondary hyperaldosteronism through this mechanism:

- Congestive heart failure
- Constriction of the vena cava
- Hepatic cirrhosis

Table X-4-3. Summary of the Preceding Concerning Secondary Hyperaldosteronism

The cause in all cases is a **decrease** in blood pressure.	
1. Plasma renin and angiotensin II activity: The increased angiotensin II activity will drive the secondary hyperaldosteronism.	↑
2. Total body sodium:	↑
3. ECF volume:	↑
4. Plasma volume:	↑
5. Edema*:	yes

*Na^+ escape prevents peripheral edema in primary but not secondary hyperaldosteronism. Also note that the increased ECF volume remains mainly on the venous side of the circulation, accentuating the venous congestion and preventing a return of circulating blood volume to normal.

ENZYME DEFICIENCIES

Single enzyme defects can occur as congenital "inborn errors of metabolism." Congenital defects in any of the enzymes lead to **deficient cortisol secretion** and the syndrome called *congenital adrenal hyperplasia.* Hyperplasia is caused by the excessive secretion of ACTH that results from the loss of the negative feedback action of cortisol. In all of the following examples, assume the deficiency is significant to the extent that it affects normal hormonal production but not a complete blockade.

A useful summary of enzyme deficiency conditions is that a horizontal cut of the pathway causes decreased production of all substances below the cut and increased secretion of substances above the cut. A vertical cut causes decrease of substances to the right of the cut and increase of substances to the left of the cut.

21 β-Hydroxylase Deficiency

Tissues affected: zona glomerulosa, zona fasciculata, zona reticularis

Effect in the zona glomerulosa

Blockade Point

Figure X-4-10 illustrates the blockade point in the zona glomerulosa.

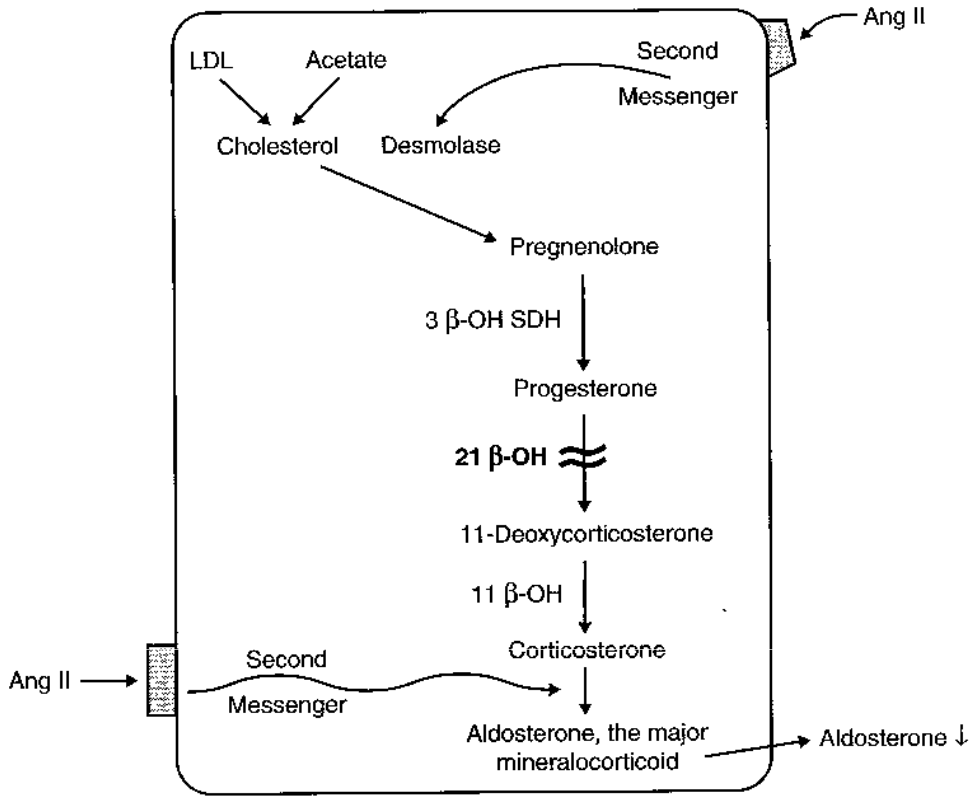


Figure X-4-10. Enzyme Deficiencies in the Zona Glomerulosa

Consequence: Result is a decreased production of aldosterone, the main mineralocorticoid.

Effect in the zona fasciculata and zona reticularis

Blockade Points

Figure X-4-11 shows the two blockade points (wavy lines) in the zona fasciculata and zona reticularis.

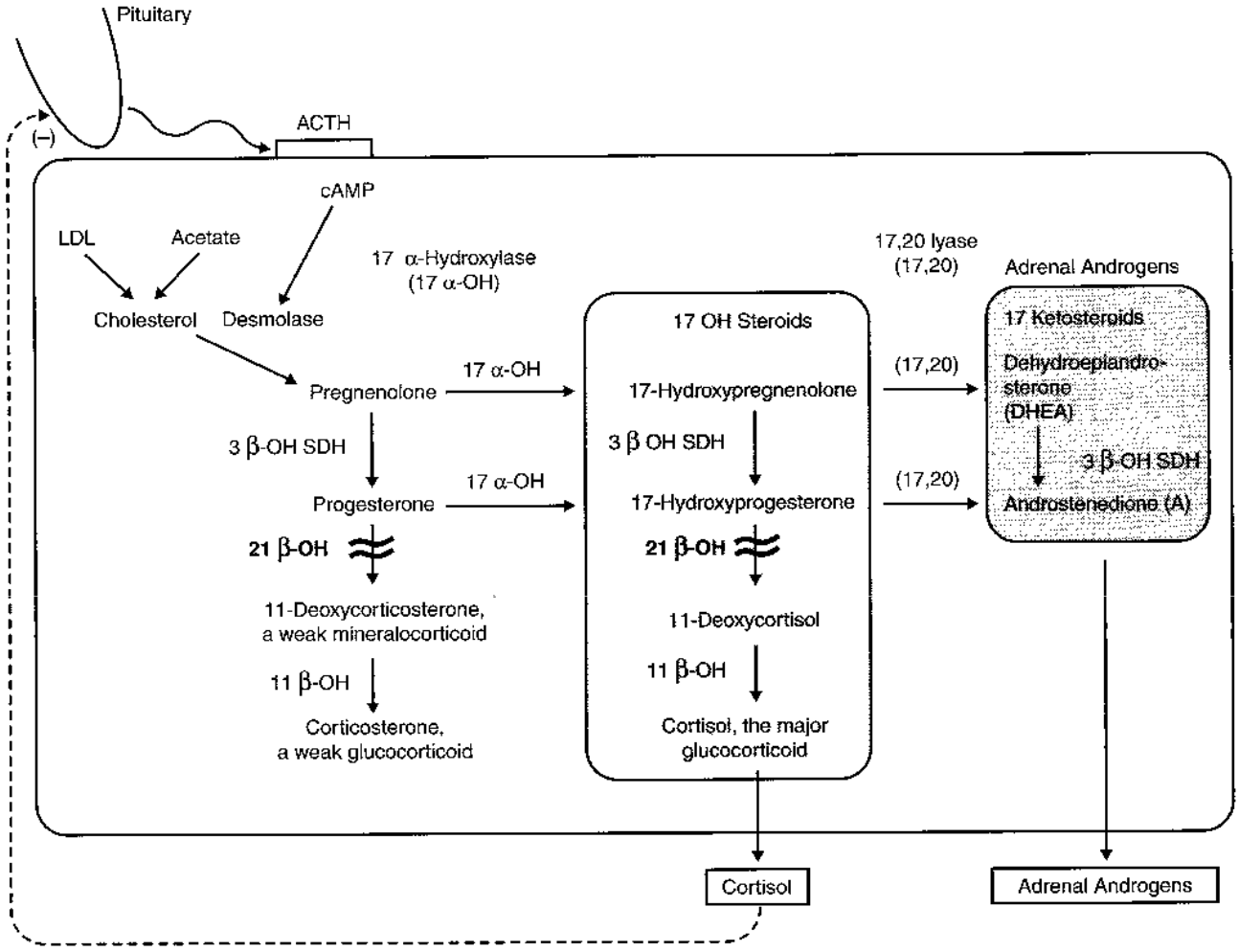


Figure X-4-11. Enzyme Deficiencies in the Zona Fasciculata and Zona Reticularis

Summary of overall pathway changes:

- Zona glomerulosa: decreased aldosterone
- Zona fasciculata, reticularis: decreased production of 11-deoxycorticosterone, a weak mineralocorticoid.
- Therefore, a mineralocorticoid deficiency, loss of Na^+, volume and a hypotensive state.
- Increased renin secretion and increased circulating angiotensin II.
- Decreased production of corticosterone, a weak glucocorticoid, and cortisol.
- Therefore, glucocorticoid deficiency and increased ACTH, which drive increases in adrenal androgen secretion

11 β-Hydroxylase Deficiency

Tissues affected: zona fasciculata, zona reticularis, zona glomerulosa

Effect in the zona fasciculata and zona reticularis

Blockade

Figure X-4-12 illustrates the blockade in the zona fasciculata and zona reticularis.

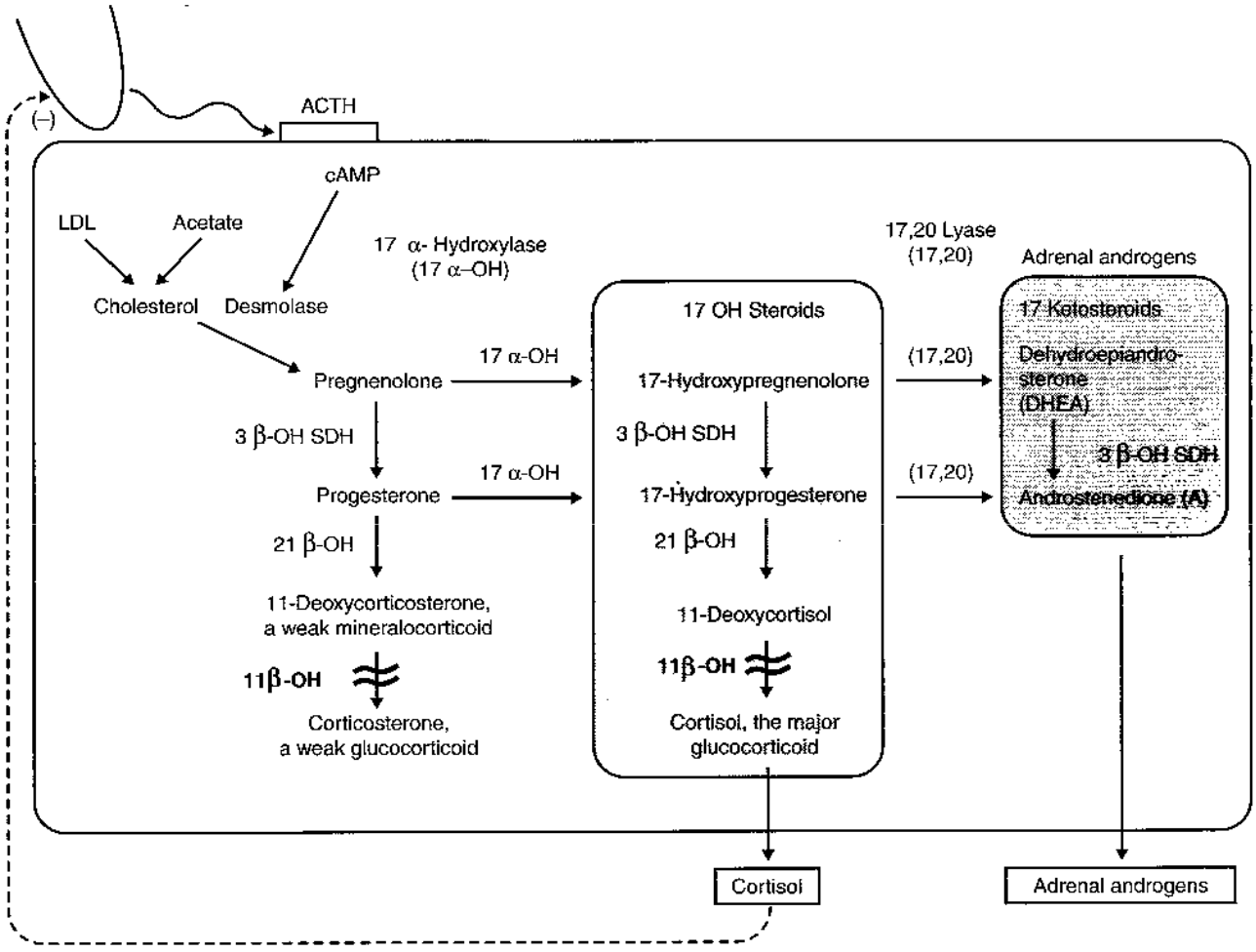


Figure X-4-12. 11-β-Hydroxylase Deficiency in the Zona Fasciculata and Zona Reticularis

Effect in the zona glomerulosa

Figure X-4-13 illustrates the effect on the zona glomerulosa.

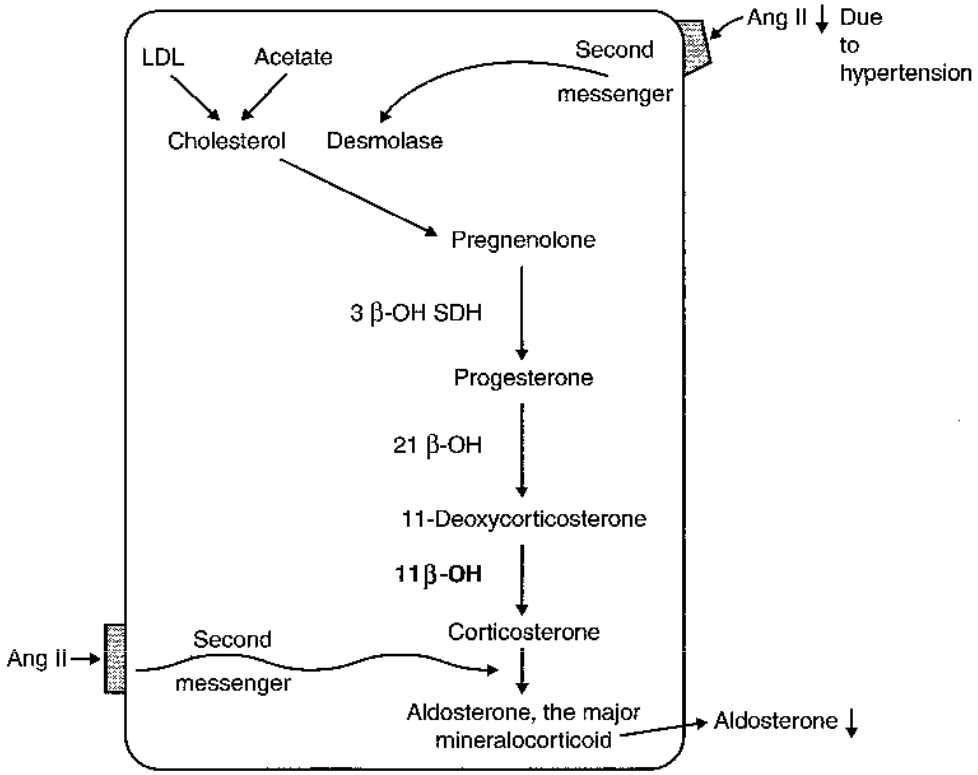


Figure X-4-13. 11-β-Hydroxylase Deficiency in the Zona Glomerulosa

Summary of overall pathway changes:

- Zona fasciculata, reticularis: decreased corticosterone and cortisol, increased ACTH and overproduction of steroids above the blockade, including:
  - Androgens and the consequences in women and prepubertal males
  - 11-deoxycorticosterone, a mineralocorticoid that leads to hypertension and a decrease in circulating angiotensin II
- Zona glomerulosa: decreased stimulation of the steroid pathway and aldosterone production due to the hypertensive decrease in circulating angiotensin II

17 α-Hydroxylase Deficiency

Tissues affected: zona fasciculata, zona reticularis, testis, ovary

Blockade in the adrenal zona fasciculata and the zona reticularis

Figure X-4-14 illustrates the blockade points in the zona fasciculata and zona reticularis.

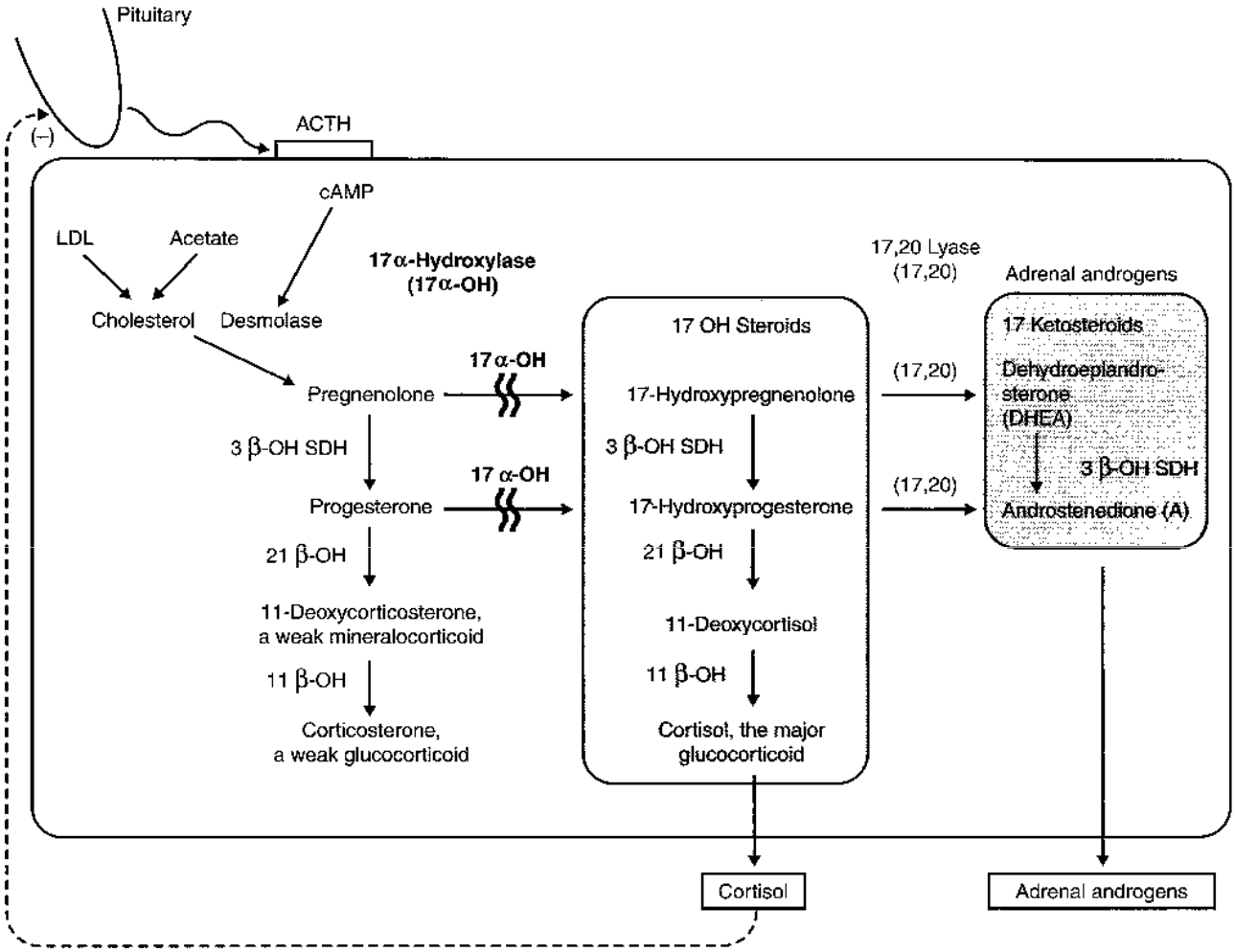


Figure X-4-14. 17 α-Hydroxylase Deficiency

Summary of overall pathway changes:

- Zona fasciculata, reticularis: decreased adrenal androgens, decreased cortisol, and increased ACTH. Increased 11-deoxycorticosterone leading to hypertension. The reduced circulating angiotensin II reduces stimulation of zona glomerulosa and aldosterone secretion.

Effect in the testes

Figure X-4-15 illustrates the blockade points in the testes.

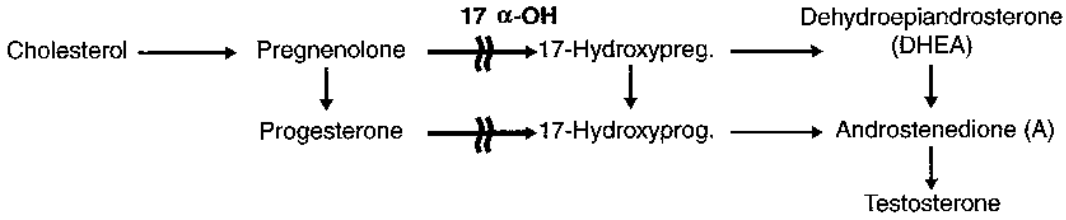


Figure X-4-15. Testicular 17 α-OH Deficiency

Summary
Decreased production of all androgens including testosterone

Effect in the ovaries

Figure X-4-16 illustrates the blockade points in the ovaries.

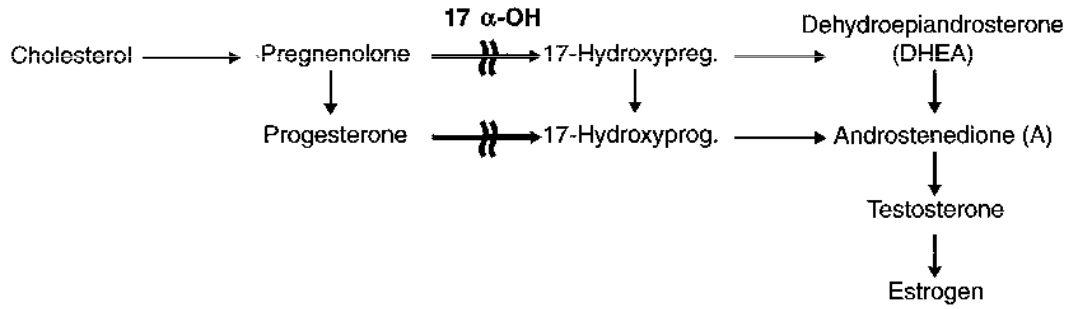


Figure X-4-16. Ovarian 17 α-OH Deficiency

Summary
Decreased production of estrogens and androgens

Summary

Table X-4-4. Summary of Enzyme Deficiencies

Deficiency	Glucocorticoid	ACTH	Blood Pressure	Mineralocorticoid		Androgen	Estrogen
				Aldo	DOC		
21 β-OH	↓	↑	↓	↓	↓	↑ adrenal	_
11 β-OH	↓	↑	↑	↓	↑	↑ adrenal	_
17 α-OH	↓	↑	↑	↓	↑	↓ adrenal & testicular	↓

Note: In all three disorders, there will be a deficiency in cortisol and an increase in circulating ACTH. The ACTH is responsible for the adrenal hyperplasia.

Consequences of Congential Adrenal Hyperplasia

21 β-Hydroxylase deficiency

- Accounts for about 90% of the cases
- 75% of the cases have mineralocorticoid deficiency
- Neonates may present with a salt-wasting crisis.
- Salt wasters tend to have hyponatremia, hyperkalemia, and raised plasma renin.
- 17-hydroxyprogesterone is elevated.
- Increased androgens lead to virilization of the female fetus and sexual ambiguity at birth
- Males are phenotypically normal at birth but develop precocious pseudopuberty, growth acceleration, premature epiphyseal plate closure, and diminished final height.
- Goal in treatment is to bring glucocorticoid and mineralocorticoid back to the normal range which would also suppress adrenal androgen secretion.

11 β-Hydroxylase deficiency

- Accounts for about 7% of all cases
- Clinical features of increased androgens similar to the preceding form, including virilization of female fetus.
- The principal difference with this form is the hypertension produced by 11-deoxycorticosterone, along with hypokalemia and suppressed renin secretion.
- Milder forms do not present with hypertension and its consequences.

17 α-Hydroxytlase deficiency

- Extremely rare
- Usually diagnosed at the time of puberty when the patient presents with hypertension, hypokalemia, and hypogonadism
- Individuals have eunuchoid characteristics.

Chapter Summary

* Loss of mineralocorticoid function causes severe hypotension and can be fatal. Lack of glucocorticoids is not life-threatening under normal conditions, but stressful situations can cause severe problems.
* Loss of pituitary function causes loss of glucocorticoids but not mineralocorticoids.
* Cortisol, aldosterone and adrenal androgens can be easily measured in plasma and urine.
* Sulfated androgen is specific to synthesis in the adrenals.
* Zona glomerulosa main stimulus is AII and secretion is aldosterone.
* Zona fasciculata and reticularis main stimulus is ACTH and main secretions are cortisol and androgens. Weak mineralocorticoid and glucocorticoid normally unimportant.
* Cortisol is a stress hormone that mobilizes carbohydrate, protein and lipid. Other stress hormones include growth hormone, glucagon, and epinephrine.
* Stress hormones are counter-regulatory because they raise plasma glucose.
* Aldosterone's main action is to increase sodium reabsorption in the kidney. Because the water follows the sodium, aldosterone does not affect sodium concentration.
* Aldosterone also increases potassium and hydrogen loss by the kidney.
* The renin-angiotensin-aldosterone system represents the long-term regulation of blood pressure. Activation is a decrease in blood pressure inside the kidney.
* Cushing's syndrome is hypercortisolism.
* Primary hypercortisolism is usually an adrenal adenoma secreting cortisol. ACTH, adrenal androgens decrease.
* Secondary hypercortisolism is due to an increase in ACTH. If the source is the anterior pituitary it is Cushing's disease. Ectopic ACTH hypersecretion is most often due to small cell carcinoma of the lung.
* Primary hypocortisolism is usually associated with Addison's disease and a concurrent loss of mineralocorticoid, increased ACTH, renin and hyperpigmentation.
* Secondary hypocortisolism is due to withdrawal of glucocorticoid therapy or an anterior pituitary mass with the loss of ACTH.
* Primary hyperaldosteronism (Conn's) due to an adenoma or hyperplasia of the zona glomerulosa. Hypertension, hypokalemia, alkalosis, low renin, and no edema (sodium escape).
* Secondary hyperaldosteronism with hypertension usually has a renal vascular origin. Hypertension, hypokalemia, and high renin.
* Secondary hyperaldosteronism with hypotension usually due to a low cardiac output. Low blood pressure, hyponatremia, and edema (no sodium escape).
* In congenital adrenal hyperplasia, decreased cortisol synthesis causes increased ACTH
* In 21 β-hydroxylase deficiency there is mineralocorticoid deficiency, salt wasting and hypotension, androgen excess and female virilization.
* In 11 β-hydroxylase deficiency there is mineralocorticoid excess, salt retention and hypertension, androgen excess as in the preceding.
* In 17 α-hydroxylase deficiency there is mineralocorticoid excess, adrenal androgen deficiency, and hypertension but gonadal steroid deficiency and hypogonadism.

Adrenal Medulla

GENERAL FEATURES OF ADRENAL MEDULLARY SECRETION

- Secretion of the adrenal medulla is 20% norepinephrine and 80% epinephrine.
- Phenylethanolamine-N-methyltransferase (PMNT) converts norepinephrine into epinephrine.
- Half-life of the catecholamines is only about 2 minutes. Metabolic endproducts include metanephrines and vanillylmandelic acid (VMA) both of which can be measured in plasma and urine
- Removal of the adrenal medulla reduces plasma epinephrine to very low levels but does not alter plasma norepinephrine. Most circulating norepinephrine arises from postganglionic sympathetic neurons.
- Because many of the actions of epinephrine are also mediated by norepinephrine, the adrenal medulla is not essential for life.
- The vasoconstrictive action of norepinephrine is essential for the maintenance of normal blood pressure, especially when an individual is standing. Plasma norepinephrine levels double when one goes from a lying to a standing position. People with inadequate production of norepinephrine suffer from orthostatic hypotension.
- Epinephrine is a stress hormone and rapidly increases in response to exercise, exposure to cold, emergencies, and hypoglycemia.

MAJOR METABOLIC ACTIONS OF EPINEPHRINE

- Liver: Epinephrine increases the activity of liver and muscle phosphorylase, promoting glycogenolysis. This increases glucose output by the liver.
- Skeletal muscle: Epinephrine promotes glycogenolysis but because muscle lacks glucose-6-phosphatase, glucose cannot be released by skeletal muscle; instead, it must be metabolized at least to lactate before being released into the circulation.
- Adipose tissue: Epinephrine increases lipolysis in adipose tissue by increasing the activity of hormone-sensitive lipase. Glycerol from TG breakdown is a minor substrate for gluconeogenesis.
- Epinephrine increases the metabolic rate. This will not occur without thyroid hormones or the adrenal cortex.

Summary of the Metabolic Actions of Epinephrine on CHO and Fat

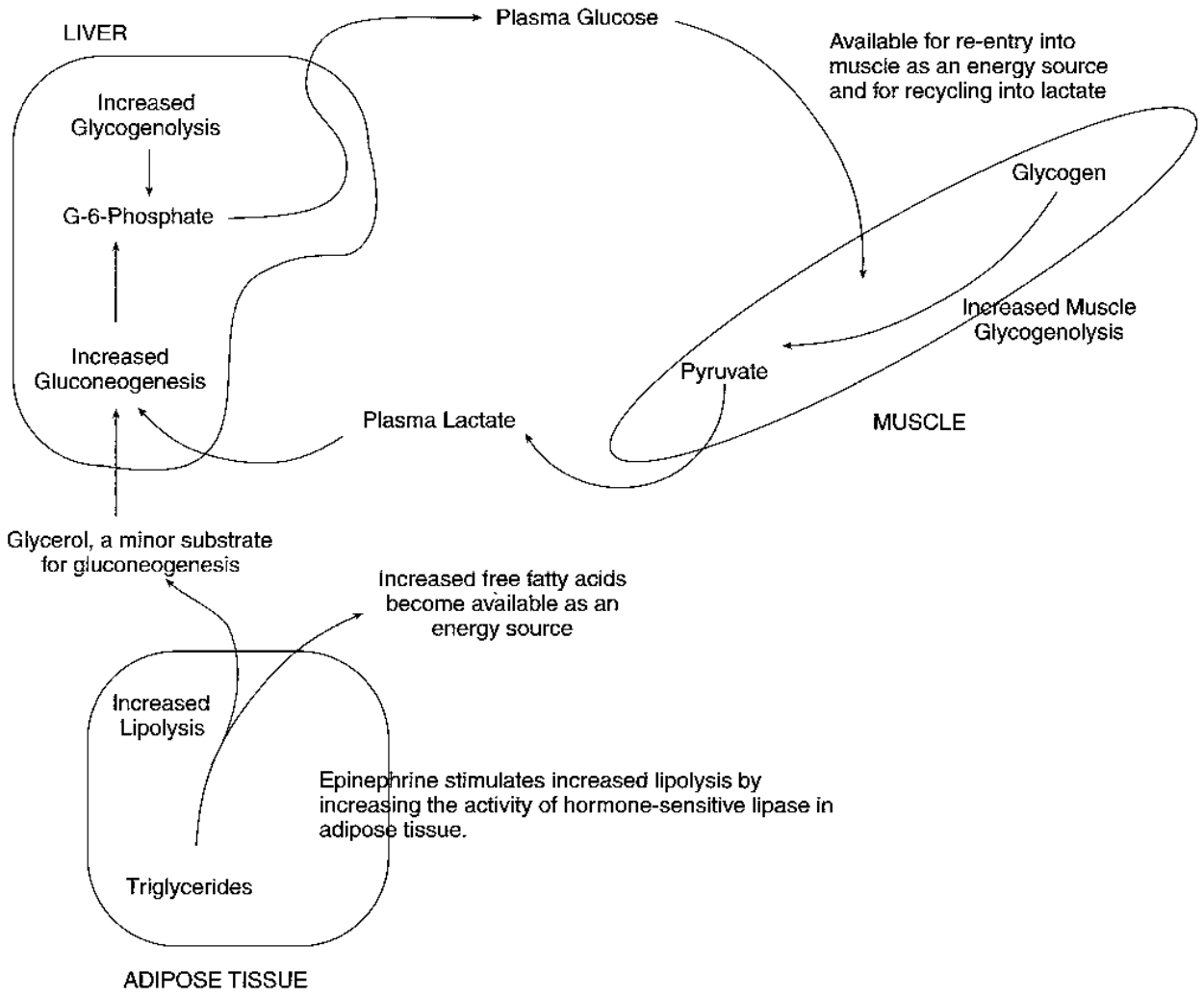


Figure X-5-1. Actions of Catecholamines

PHEOCHROMOCYTOMAS

- Adrenal tumors that secrete epinephrine and norepinephrine in various ratios
- Usually unilateral benign tumors
- Characteristic of MEN 2A and MEN 2B
- Paragangliomas are extrarenal pheochromocytomas of sympathetic ganglia located primarily within the abdomen and that secrete norepinephrine.
- Most consistent feature is hypertension. Symptoms include headache, diaphoresis, palpitations, and anxiety. Increased metabolic rate and hyperglycemia also occur.
- Pheochromocytomas are highly vascular and encapsulated.
- Episotic release of hormone, particularly when it is mainly norepinephrine, can abruptly cause a hypertensive crisis. Can be induced by physical stimuli that displaces abdominal contents.
- Most reliable screening is plasma or urine metanephrines.
- Usually curable but can be fatal if undiagnosed

Chapter Summary

* Circulating epinephrine originates mainly from the adrenals, whereas circulating norepinephrine originates mainly from sympathetic nerve endings.
* Epinephrine is a stress hormone secreted in response to exercise, exposure to cold, emergencies, and hypoglycemia.
* Epinephrine increases blood glucose via liver glycogenolysis. It also stimulates muscle glycogenolysis, but muscle does not release glucose.
* Epinephrine increases the release of fatty acids from adipose tissue by increasing the activity of hormone-sensitive lipase.
* Pheochromocytomas secrete epinephrine and norepinephrine and are most consistently associated with hypertension.
* Episotic release, particularly of norepinephrine, can induce a hypertensive crisis.
* The most reliable screening is metanephrines.

Endocrine Pancreas

ORGANIZATION AND SECRETION OF THE ISLETS OF LANGERHANS

The location and proportion of each major hormone-secreting cell type of the islets of Langerhans are shown in Figure X-6-1. The local inhibitory paracrine action of each islet hormone is shown by dashed arrows. The diameter of each circle approximately represents the proportion of that cell type present in the islets.

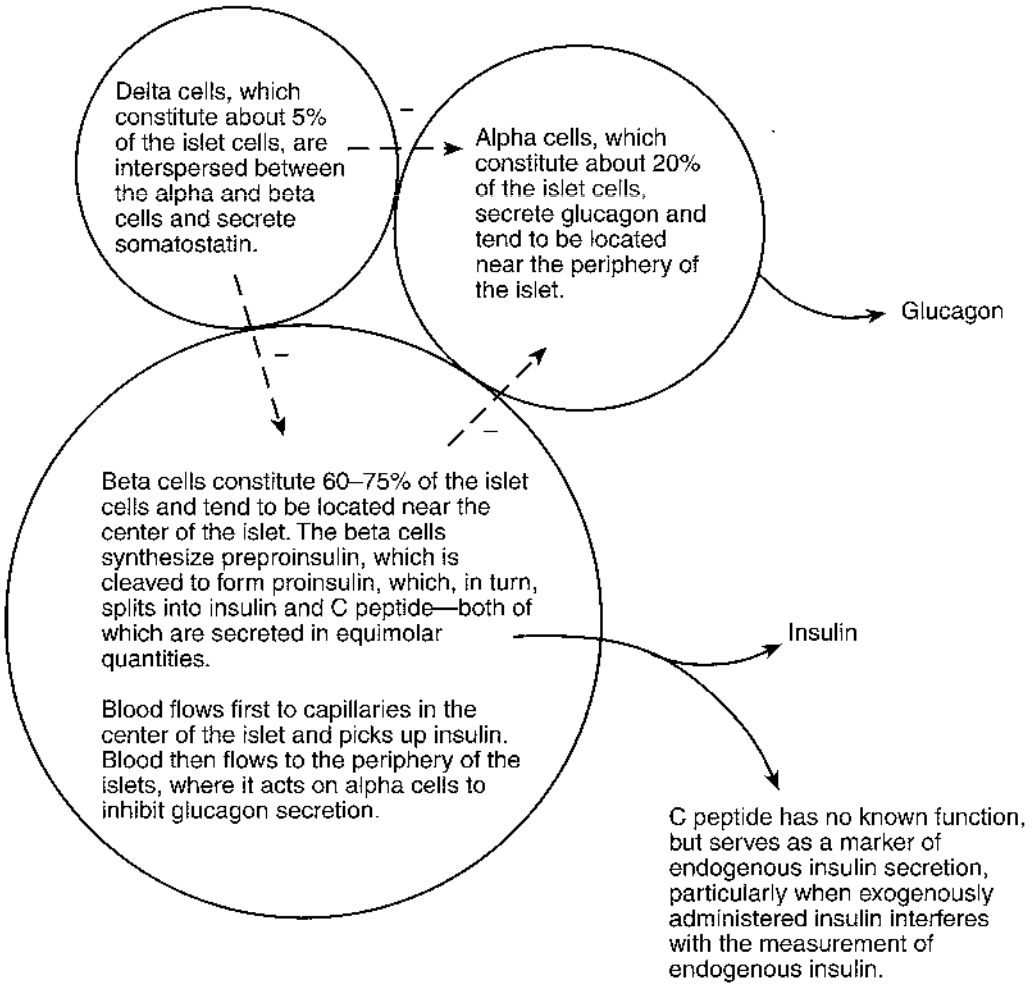


Figure X-6-1. Hormones of the Pancreatic Islets

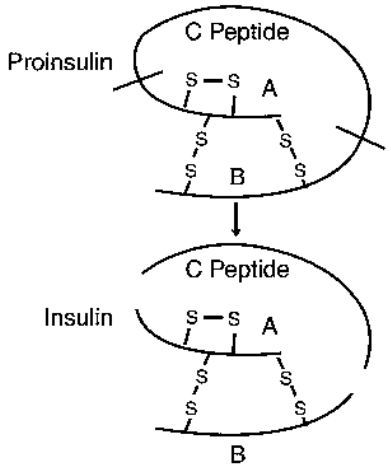


Figure X-6-2. Insulin

ACTIONS OF INSULIN

The Insulin Receptor

- The portion of the insulin receptor that faces externally has the hormone-binding domain.
- The portion of the insulin receptor that faces the cytosol has tyrosine kinase activity.
- When occupied by insulin, the receptor phosphorylates itself and other proteins. (See Step 1 Biochemistry Lecture Notes for additional details.)

Peripheral Uptake of Glucose

Glucose is taken up by peripheral tissues by facilitated transport (a passive transport not linked to sodium). Insulin facilitates this uptake in some tissues. Typically the insulin receptor causes the insertion of glucose transporters in the membrane.

Tissues that require insulin for effective uptake of glucose are:

- Adipose tissue
- Resting skeletal muscle (although glucose can enter working muscle without the aid of insulin)

Tissues in which glucose uptake is not affected by insulin are:

- Nervous tissue
- Kidney tubules
- Intestinal mucosa
- Red blood cells
- β-cells of pancreas

Metabolic Actions of Insulin

Insulin is a major anabolic hormone, which is secreted in response to a carbohydrate- and/or protein-containing meal.

Anabolic hormones tend to promote protein synthesis (increase lean body mass). Other anabolic hormones include:

- Thyroid hormones
- Growth hormone/IGF I
- Sex steroids (androgens)

Effects of insulin on carbohydrate metabolism

Insulin increases the uptake of glucose and its metabolism in muscle and fat. By increasing glucose uptake in muscle, its metabolism increases, i.e., its conversion to carbon dioxide and water is increased.

Insulin increases glycogen synthesis in liver and muscle. The activity of enzymes that promote glycogen synthesis (glucokinase and glycogen synthetase) is increased. The activity of those enzymes that promote glycogen breakdown (phosphorylase and glucose-6-phosphatase) is decreased.

- Glucokinase and glucose-6-phosphatase are expressed by the liver but not by muscle.

Effects of insulin on protein metabolism

- Insulin increases amino acid uptake by muscle cells.
- Insulin increases protein synthesis.
- Insulin decreases protein breakdown (deficiency of insulin results in a breakdown of protein).

Effects of insulin on fat metabolism

Insulin increases:

- Glucose uptake by fat cells (increases membrane transporters). By increasing glucose uptake, insulin also makes triose phosphates available for triglyceride synthesis in adipose tissue.
- Triglyceride uptake by fat cells. It increases the activity of lipoprotein lipase (also called extracellular or clearing factor lipase). Lipoprotein lipase is located on the endothelium of capillaries and clears VLDL and chylomicrons from the blood.
- Triglyceride synthesis (lipogenesis) in adipose tissue and liver by stimulating the rate-limiting step, namely the carboxylation of acetyl CoA to malonyl CoA. In other words, insulin stimulates the conversion of carbohydrate into fat.
- These relationships are shown schematically in Figure X-6-2.

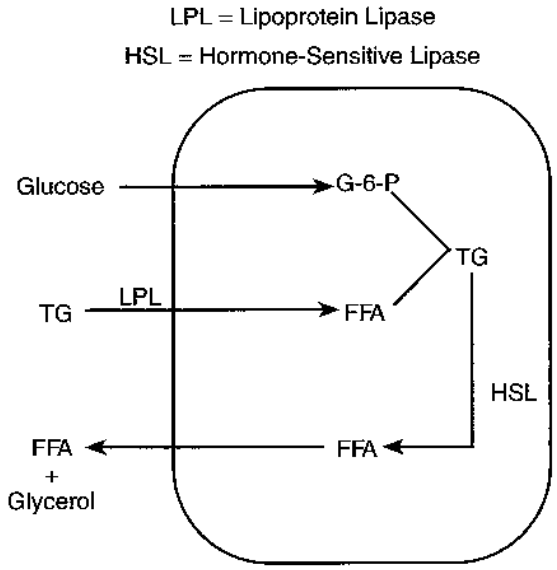


Figure X-6-3. The Adipose Cell

Insulin decreases:

- Triglyceride breakdown (lipolysis) in adipose tissue by decreasing the activity of hormone-sensitive lipase. This enzyme is activated by stress hormones (i.e., cortisol, growth hormone, epinephrine [glucagon]).
- Formation of ketone bodies by the liver.

Insulin Effects on Potassium

Insulin pumps K^+ into cells. Although the overall process is not well understood, insulin increases the activity of Na/K-ATPase in most body tissues.

This K^+-lowering action of insulin is used to treat acute, life-threatening hyperkalemia. For example, sometimes hyperkalemia of renal failure is successfully lowered by the simultaneous administration of insulin and glucose. (The glucose is given to prevent severe insulin-induced hypoglycemia from developing.)

Summary

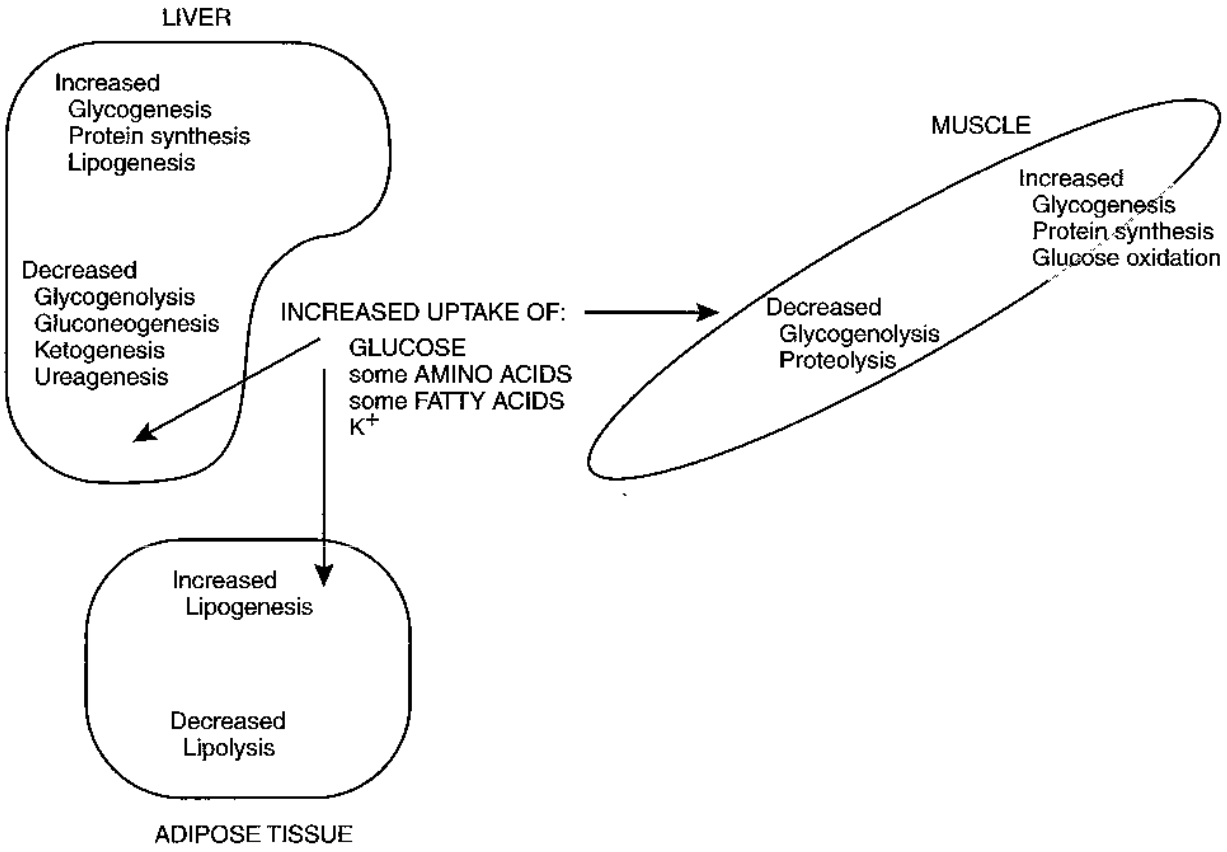


Figure X-6-4. Summary of the Major Actions of Insulin

CONTROL OF INSULIN SECRETION

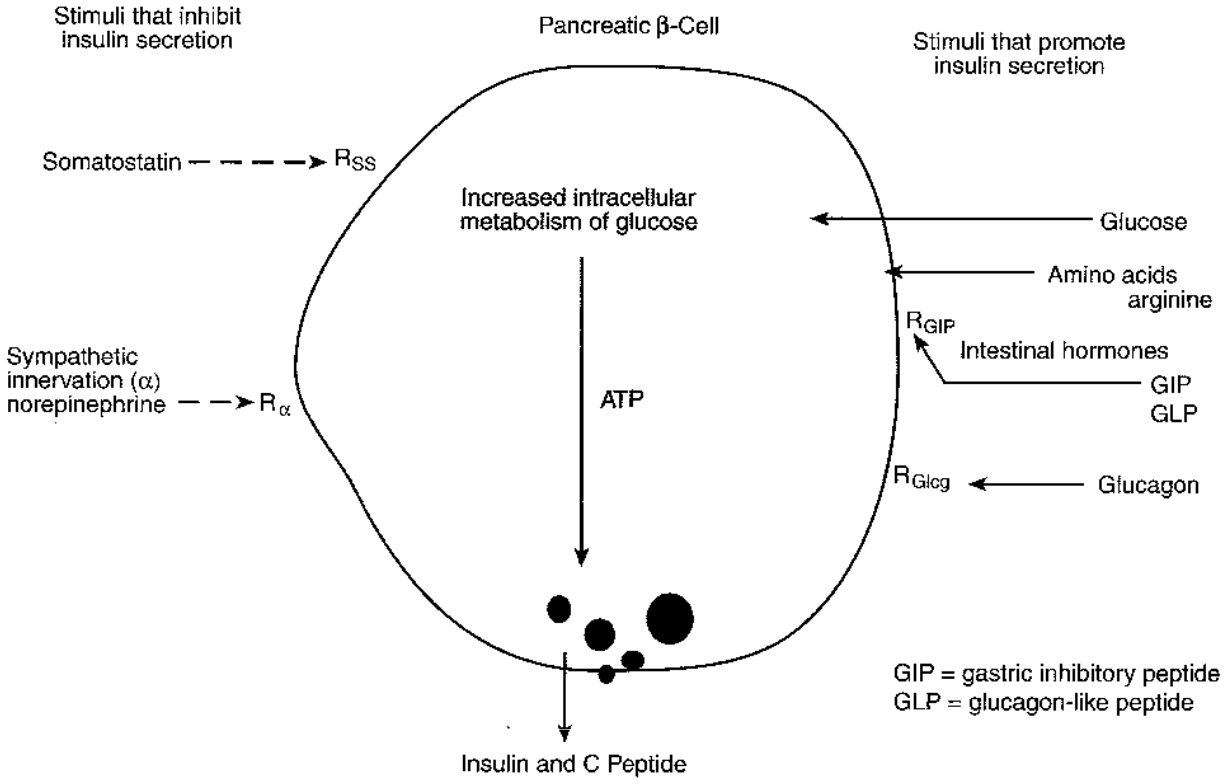


Figure X-6-5. Control of Insulin Secretion

General Features

The most important controller of insulin secretion is plasma glucose. Above a threshold of 100 mg%, insulin secretion is directly proportional to plasma glucose.

For glucose to promote insulin secretion, it must not only enter the β-cell but also be metabolized, so as to increase intracellular ATP concentration.

Increased ATP closes a potassium channel and depolarizes the β-cell; this opens voltage-dependent Ca^{2+} channels, and the increase in intracellular Ca^{2+} promotes exocytosis of insulin. Blockade of these potassium channels is a possible mechanism of some hypoglycemic drugs used for treatment of type 2 diabetes.

All of the hormones or neurotransmitters named in Figure X-6-5 attach to the membrane receptors (R). In contrast, the metabolic substrates, glucose and amino acids, enter the β-cell.

ACTIONS OF GLUCAGON

Overview

Glucagon is a peptide hormone.

Glucagon is secreted by the α-cells of the pancreatic islets. The primary target for glucagon action is the liver hepatocyte, where its action is mediated by an increase in the concentration of cAMP. The cAMP activates protein kinase A, which, by catalyzing phosphorylation, alters the activity of enzymes mediating the actions given below.

Note: Skeletal muscle is not a target tissue for glucagon.

Specific Actions of Glucagon on the Liver

1. Increases liver glycogenolysis.

   Glucagon activates glycogen phosphorylase, breaking down glycogen to glucose-1-phosphate. Glucagon inactivates glycogen synthetase, preventing the glucose-1-phosphate from being recycled back into glycogen.

2. Increases liver gluconeogenesis.

   Glucagon promotes the conversion of pyruvate to phosphoenolpyruvate. Glucagon increases the conversion of fructose-1, 6-biphosphate to fructose-6-phosphate.

3. Increases liver ketogenesis and decreases lipogenesis.

   Glucagon inhibits the activity of acetyl CoA carboxylase, decreasing the formation of malonyl CoA. When the concentration of malonyl CoA is low, ketogenesis is favored over lipogenesis.

4. Increases ureagenesis.

   By increasing the production of glucose from pyruvate, glucagon indirectly stimulates the transamination of alanine to pyruvate. The amino group is eliminated as urea.

5. Increases insulin secretion.

   The amino acid sequence of glucagon is similar to that of the duodenal hormone, secretin. Like secretin (and most other gut hormones), glucagon stimulates insulin secretion.

6. Increases lipolysis in the liver.

   Glucagon activates hormone-sensitive lipase in the liver, but because the action is on the liver and not the adipocyte, glucagon is not considered a major fat-mobilizing hormone.

Control of Glucagon Secretion

Major factors that control glucagon secretion are summarized in Figure X-6-6. Stimuli that promote glucagon secretion are depicted on the right, and those that inhibit on the left. R designates a surface receptor for the particular hormone or neurotransmitter.

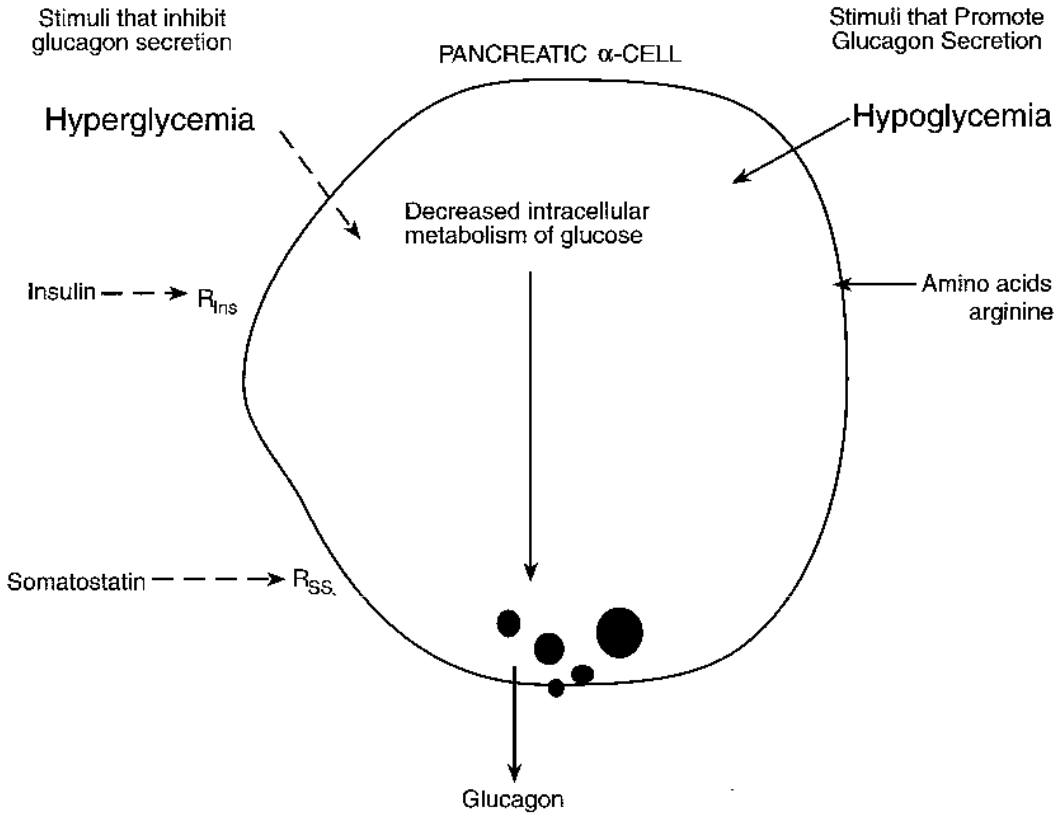


Figure X-6-6. Control of Glucagon Secretion

Further information

Low plasma glucose (hypoglycemia) is the most important physiologic promoter for glucagon secretion, and elevated plasma glucose (hyperglycemia) the most important inhibitor.

Amino acids, especially dibasic amino acids (arginine, lysine), also promote the secretion of glucagon. Thus, glucagon is secreted in response to the ingestion of a meal rich in proteins.

Overall view of glucose counterregulation

Glucose counterregulation is the concept that plasma glucose concentration is regulated by insulin and by hormones that oppose, or counter, its actions. Figure IX-6-7 displays a feedback diagram of some of the interaction of insulin and glucagon on plasma glucose concentration, as well as fat and protein metabolism.

Summary

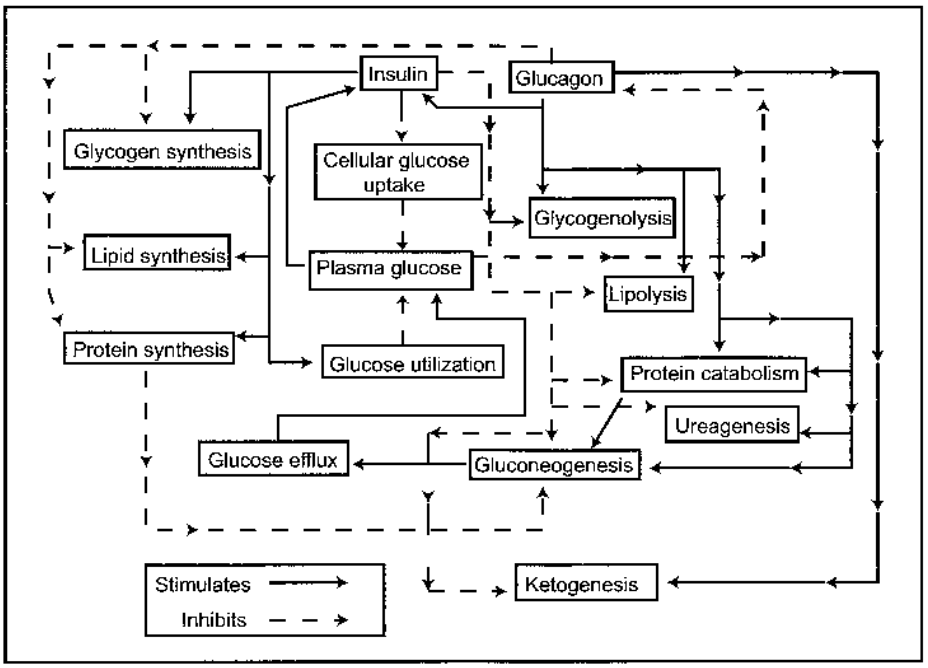


Figure X-6-7. Insulin Actions in Liver

Insulin : Glucagon Ratio

- Insulin and glucagons move substrates in opposite directions. The direction of substrate fluxes is very sensitive to this ratio.
- Normal postabsorptive, ratio 2.0
- States requiring mobilization of substrates, ratio .5 or less
- Carbohydrate meal, ratio 10 or more
- Protein meal or fat meal produces little change in the ratio.

DIABETES MELLITUS

In both types of diabetes mellitus, there is hyperglycemia, polyuria, increased thirst and fluid intake, hyperosmolar state, recurrent blurred vision, mental confusion, lethargy, weakness, and abnormal peripheral sensation. Coma, if it does occur, is due to the hyperosmotic environment, not the acidosis.

Type 2

- Accounts for about 90% of all the cases of diabetes
- Strong genetic component
- Body build is usually obese (particularly central or visceral).
- Usually, but not always, middle-aged or older
- The number of younger individuals in this category is increasing.

- Characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic output of glucose. Insulin resistance precedes secretory defects and in the early stages hyperinsulinemia is able to overcome tissue resistance. Ultimately beta cell failure can occur.
- Insulin levels may be high, normal, or low.
- Resistance to insulin is not well understood. It is thought to be due to postreceptor defects in signaling, which ultimately lead to a decrease in the number of glucose transporters. Reducing plasma glucose and thus plasma insulin can increase receptor sensitivity toward normal.
- Plasma glucose good screening for type 2. Elevated glucose due to elevated hepatic output.
- With a controlled diet, the symptoms of type 2 diabetes often disappear without the necessity for pharmacologic therapy.
- Individuals tend to be ketosis resistant. The presence of some endogenous insulin secretion appears to protect from development of a ketoacidosis. If it does develop, it is usually the result of severe stress or infection (increased counterregulatory homones, suppressed insulin).
- In nonobese patients, a deficient insulin release by the pancreas is often the problem, but varying degrees of insulin resistance can also occur.

Metabolic Syndrome (Syndrome X)

A group of metabolic derangements that includes atherogenic dyslipidemia (low HLD) and high triglycerides, elevated blood glucose, hypertension, central obesity, prothrombotic state, and a proinflammatory state. The clustering of these risk factors increases the probability of developing cardiovascular disease and type 2 diabetes.

Type 1

- Genetic association less marked than in type 2
- Generally results from an infection or environmental insult to genetically predisposed individuals whose immune system destroys the pancreatic beta cells
- Symptoms do not become evident until 80% of the beta cells are destroyed.
- Body build usually lean
- Usually, but not always, early in onset
- Due to an absence of insulin production
- Increased glucagon secretion also generally occurs
- Three target tissues for insulin—liver, skeletal muscle, and adipose tissue—fail not only to take up absorbed nutrients but also to deliver inappropriate high levels to the bloodstream. This would include glucose, amino acids, and fatty acids.

Metabolic effects in insulin-deficient individuals

CHO

- Increased blood glucose concentration
- Increased glycogen breakdown
- Decreased peripheral glucose use

Protein

- Increased protein breakdown
- Increased catabolism of amino acids
- Increased gluconeogenesis
- Increased ureagenesis
- Decreased protein synthesis

Fat

- Increased triglyceride breakdown
- Increased level of circulating free fatty acids
- Increased ketosis, resulting in ketoacidosis (metabolic acidosis)
- Decreased fatty acid synthesis
- Decreased triglyceride synthesis

Renal System

The failure to reabsorb all the filtered glucose in the proximal tube also prevents normal water and electrolyte reabsorption in this segment, resulting in the loss of electrolytes along with the water and glucose. This includes both sodium and potassium. Thus, in the polyuria there is increased excretion of sodium and potassium, even though urine concentration of electrolytes is low.

Potassium Ion

- Intracellular concentration is low.
- Hydrogen ions move intracellularly to be buffered, and potassium ions leave the cell.
- There is a lack of the normal insulin effect of pumping potassium ion into cells.
- Plasma levels may be increased, normal, or even decreased, depending in part on the renal handling of potassium. Even though plasma levels may be above normal, total body potassium is usually below normal due to polyuria and dehydration.
- Sudden insulin replacement can produce severe hypokalemia, and potassium replacement is a normal part of therapy.

Sodium Ion

- Polyuria decreases total body sodium but dehydration may keep sodium within or close to the normal range.
- Hyperosmolar state due to the hyperglycemia. Thus, 2 times the sodium concentration is not a good index of osmolarity.

$$\text{Effective osmolarity} = 2\,(\text{Na})\ \text{mEq/L} + \text{glucose mg/dL divided by } 18$$

Hyperosmolar Coma

- Severe hyperglycemia shifts fluid from the intracellular to the extracellular space.
- Polyuria decreases volume of the extracellular space and leads to a decreased renal plasma flow and a reduced glucose excretion. Combined with the rise in counterregulatory hormones, the plasma glucose rises further.
- The severe loss of intracellular fluid from the brain causes the coma.
- Type 2 diabetics often present with the highest plasma glucose and greater states of dehydration. Thus these patients have a higher incidence of coma.

Diabetic Ketoacidosis

- Without any insulin, excessive lipolysis provides fatty acids to the liver, where they preferentially converted to ketone bodies because of the unopposed action of glucagon.
- Blood pH and bicarbonate decrease due to the metabolic acidosis.
- Increased hydrogen ion secretion (collecting duct) and the formation of an acid urine will occur as a compensation for the ketoacidosis. The hydrogen ion secretion will tend to diminish potassium secretion, but the higher than normal tubular flow will promote potassium secretion.
- Increased alveolar ventilation partially compensates for the metabolic acidosis. When the arterial pH decreases to about 7.20, ventilation becomes deep and rapid (Kussmaul breathing).
- The severe acidosis is in addition to the dehydration and net decrease in total body sodium and potassium.
- Treatment is by replacement of fluid and electrolytes and administering insulin

Hypoglycemia

- Often occurs during exercise or fasting, situations normally associated with low insulin and elevated counterregulatory hormones. This would tend to raise plasma glucose. However, in the diabetic, overdosing with insulin causes hypoglycemia.
- Type 1 diabetics are particularly prone to hypoglycemia. In these individuals the glucagon response to hypoglycemia is absent.
- Initial symptoms due to catecholamine release followed by the direct effects of hypoglycemia include slowed mental processes and confusion.
- Rebound hyperglycemia can occur by excessive glucose administration.

PANCREATIC ENDOCRINE-SECRETING TUMORS

Insulinomas

- Most common islet cell tumor
- Found almost exclusively within the pancreas and hypersecrete insulin
- Most common symptoms due to the hypoglycemia (confusion, disorientation, headache)
- Association with MEN 1
- Insulin measured to determine insulin-mediated versus noninsulin-mediated hypoglycemia
- Insulin-secreting tumor: insulin and C peptide both elevated
- Factitious hypoglycemia: C peptide below normal

Other Endocrine-Secreting Tumors

- Gastrinomas
- Glucagonomas
- Somatostomas
- VIPomas

Summary

Table X-6-1. Summary of Insulin-Related Pathophysiologic States

	Glucose	Insulin	C peptide	Ketoacidosis
Type 2 diabetes	↑	↑, ↔	↑, ↔	–
Type 1 diabetes	↑	↓	↓	+
Insulinoma	↓	↑	↑	–
Factitious hypoglycemia (self-injection of insulin)	↓	↑	↓	–

Chapter Summary

* Within the islets, beta cells are in the center, while the alpha and delta cells are in the periphery.
* C peptide secreted in conjunction with insulin is an index of endogenous insulin secretion.
* The peripheral uptake of glucose is via facilitated transport. In some tissues, such as adipose and resting skeletal muscle, the number of functioning transporters is regulated by insulin.
* Insulin facilitates the metabolism of glucose to carbon dioxide and water and also its conversion to glycogen in liver and muscle.
* Insulin promotes protein synthesis and decreases protein breakdown.
* Insulin promotes lipogenesis. It inhibits lipolysis by decreasing the activity of hormone-sensitive lipase. Hyperglycemia is the major promoter of insulin secretion.
* The major target tissue for glucagon is the liver, where its primary action is glycogenolysis and increased glucose output.
* Hypoglycemia is the main promoter and hyperglycemia the main inhibitor of glucagon secretion.

Type 2 Diabetes

* Strong genetic component and accounts for at least 90% of all cases
* Body build central obese
* Insulin resistance, impaired insulin secretion, and increased hepatic output of glucose
* Fasting plasma glucose provides good screening.
* Individuals can have extremely high plasma glucose levels without ketoacidosis.

Type 1 Diabetes

* Generally autoimmune origin
* Absence of insulin secretion but elevated glucagon
* High circulating glucose (glycogen, gluconeogenesis), amino acids (protein), fatty acids (triglyceride)
* Polyuria, dehydration, and electrolyte depletion
* Ketoacidosis, Kussmaul breathing
* Insulinomas: increased insulin, increased C peptide, decreased plasma glucose

Hormonal Control of Calcium and Phosphate

GENERAL ASPECTS

- The percentage of dietary calcium absorbed from the gut is inversely related to intake.
- The dietary intake of and the percentage of calcium absorbed is diminished in the elderly.
- A constant percentage of the ingested phosphate is absorbed regardless of intake.

The approximate percentage of the body's total calcium is given for each of the compartments in Figure X-7-1. In addition, the fraction of calcium is indicated. The calcium concentration in the interstitial fluid is 103 to 104 times higher than the intracellular calcium concentration. The initiation of many cellular processes (secretion, movement of intracellular organelles, cell division) is linked to a sudden brief increase in intracellular (cytosolic) calcium.

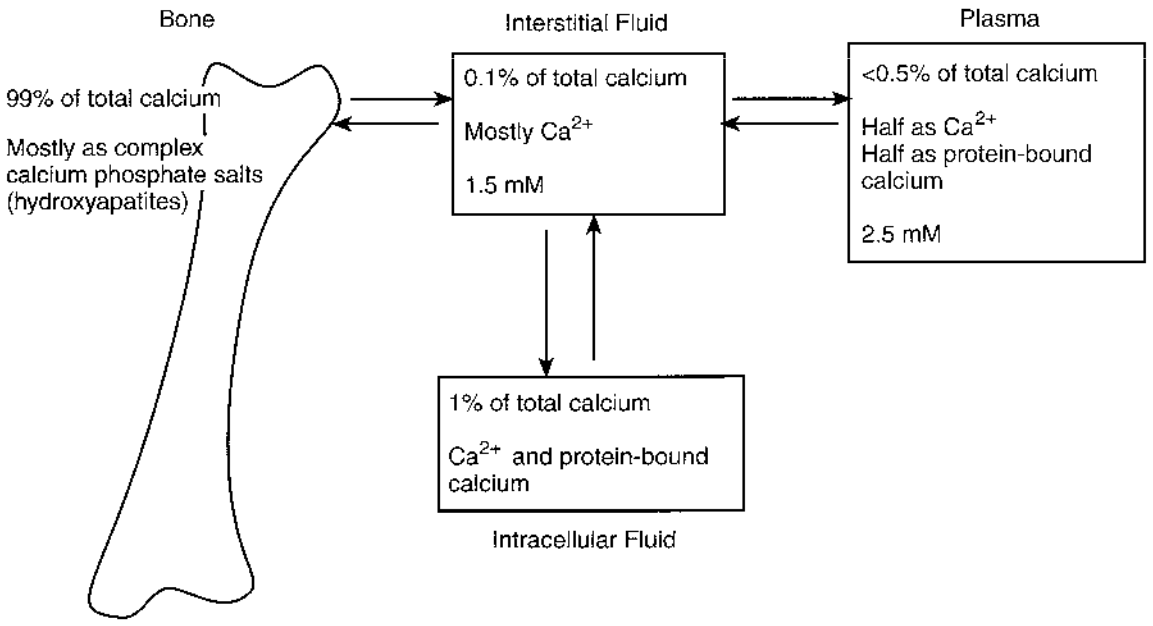


Figure X-7-1. Calcium Distribution in the Body

Plasma Calcium

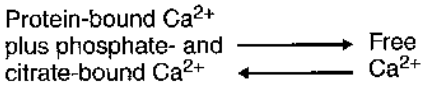


Figure X-7-2. Relationship of Bound and Free Calcium

- Plasma calcium represents 45% ionized free, 40% attached to protein, 15% associated with anions such as phosphate and citrate.
- The free calcium is the physiologically active and precisely regulated form.
- Alkalosis (hyperventilation) decreases and acidosis increases free plasma calcium by varying the amount bound to protein.
- The most accurate determination of free calcium is via a calcium-selective electrode.

Relationship Between Calcium and Phosphate

Bone is a complex precipitate of calcium and phosphate to which hydroxide and bicarbonate ions are added to make up the mature hydroxyapatite crystals, which are laid down in a protein (osteoid) matrix. Whether calcium and phosphate are laid down in bone (precipitate from solution) or are resorbed from bone (go into solution) depends on the product of their concentrations rather than on their individual concentrations.

When the product exceeds a certain number (solubility product or ion product), bone is laid down:

$$[Ca^{2+}] \times [PO_4] > \text{solubility product} = \text{bone deposition}$$

- Under normal conditions the ECF product of calcium times phosphate is close to the solubility product.
- Thus, an increase in the interstitial fluid concentration of either Ca^{2+} or phosphate increases bone mineralization.
- For example, an increase in plasma phosphate would increase the product of their concentrations, promote precipitation, and lower free calcium in the interstitial fluid.
- A malignant increase in the concentration of calcium or phosphate due to chronic renal disease or rhabdomyolysis can cause the precipitation of calcium phosphate within tissues.

When the product is below the solubility product, bone is resorbed:

$$[Ca^{2+}] \times [PO_4] < \text{solubility product} = \text{bone resorption}$$

- Thus, a decrease in the interstitial concentration of either Ca^{2+} or phosphate promotes the resorption of these salts from bone (demineralization).
- For example, a decrease in plasma phosphate alone would promote bone demineralization. Increasing renal excretion of phosphate would promote bone demineralization and a rise in interstitial free calcium.

It is the free Ca^{2+}, not the phosphate, that is regulated so precisely. Hormonal control of free Ca^{2+} levels is via a dual hormonal system; parathyroid hormone and vitamin D.

Vitamin D should be considered more of a prohormone than a vitamin.

PARATHYROID HORMONE (PTH)

General Features of PTH and Its Actions

- PTH is a peptide hormone released from the parathyroids in response to lowered interstitial free Ca^{2+}.
- In fact, the only important physiologic signal regulating release of PTH is free Ca^{2+}.
- The negative feedback relationship between plasma calcium and PTH secretion is highly sigmoidal, with the steep portion of the curve representing the normal range of plasma free calcium.
- To sense the free calcium, the parathyroid cell depends upon high levels of expression of the calcium-sensing receptor.
- In most cells exocytosis depends on a rise in intracellular free calcium. In the parathyroids that role is taken by magnesium.
- Depletion of magnesium stores can create a reversible hypoparathyroidism.

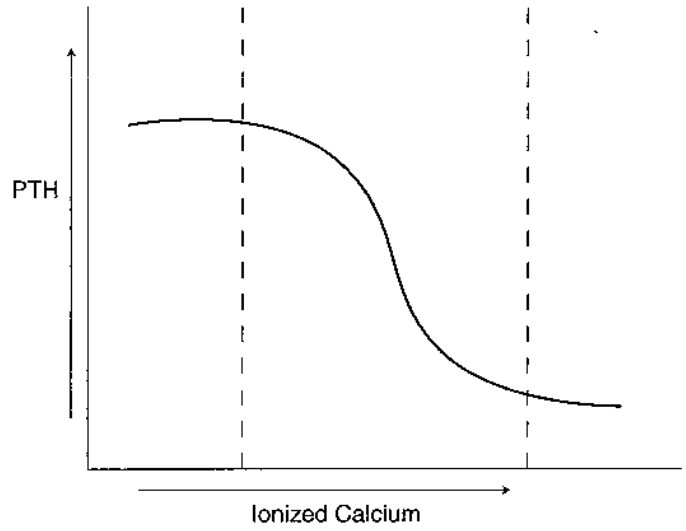


Figure X-7-3. Relationship between Plasma Calcium and PTH. Normal range is the region between the dashed line.

Figure X-7-3 shows the relationship between the ECF ionized calcium and the plasma PTH. Note that the steepest part of the sigmoid curve is within the normal ionized calcium concentration. A small change in ECF calcium causes a response in PTH secretion within seconds.

Actions of PTH

A decrease in the free calcium is the signal to increase PTH secretion and the function of PTH is to raise free calcium, which it does by several mechanisms. Some are fast-acting; others act more slowly.

Rapid actions of PTH

PTH increases Ca^{2+} reabsorption in the distal tubule of the kidney and decreases phosphate reabsorption in the proximal tubule. By decreasing renal phosphate reabsorption, PTH lowers plasma phosphate. This causes the product of the Ca^{2+} and phosphate concentrations to be less than the solubility product. This, in turn, promotes the resorption of these ions from bone and raises their concentration in the circulating blood.

Bone is immersed in a saturated aqueous solution of calcium and phosphate ions (the bone's interstitial fluid). This pool of calcium is separated from but readily exchanges with the ECF via the osteocytes, lining cells, and osteoblasts. The exchange process is summarized in Figure X-7-4.

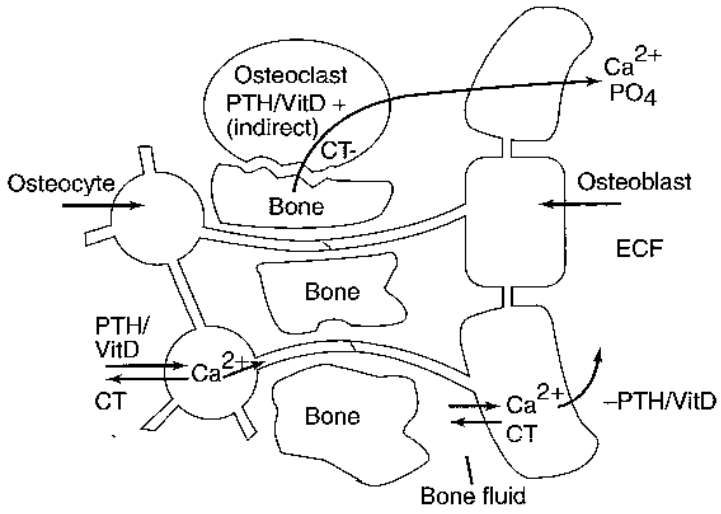


Figure X-7-4. Bone and Calcium Homeostasis

In addition, osteocytes connected to the surface cells can transfer calcium from the surface of interior bone to the bone surface and ECF. This is referred to as osteocytic osteolysis. This does not decrease bone mass but removes calcium from the most recently formed crystals. Bone resorption in addition to removing calcium destroys the collagen matrix.

Osteoblasts deposit bone and arise from cells of mesenchymal origin. They synthesize and extrude the collagen whose fibers form the organic matrix. Osteoblasts also regulate the deposition of the calcium phosphate. They can eventually differentiate into osteocytes or lining cells. Osteoblasts have receptors for PTH and vitamin D. **Osteocytes** are osteoblasts that become entrapped within mineralized bone during bone growth or remodeling. They develop multiple processes (canaliculi) which communicate with other osteocytes and surface osteoblasts. **Osteoclasts** resorb bone and arise from monocytes; several fuse to form the multinucleated osteoclasts. Osteoblasts stimulate the formation and activation of osteoclasts via signal molecules. Osteoclasts have receptors for calcitonin.

Slower actions of PTH

PTH slowly increases the formation and activity of osteoclasts, which resorb bone, releasing Ca^{2+}.

PTH increases the formation of 1,25 di-OH D3 (active vitamin D) in the proximal tubules of the kidney, which leads to increased absorption of Ca^{2+} and phosphate from the small intestine.

CALCITONIN

- Calcitonin (CT) is a peptide hormone secreted by the parafollicular cells (C cells) of the thyroid gland. It is released in response to elevated free calcium.
- Calcitonin lowers plasma calcium by decreasing the activity of osteoclasts, thus decreasing bone resorption. Calcitonin is useful in the treatment of Paget's disease.
- Calcitonin is not a major controller of Ca^{2+} in humans. Removing the thyroid (with the C cells) or excess of calcitonin via a C cell tumor (medullary carcinoma of the thyroid) has little impact on plasma calcium.

PARATHYROID HORMONE-RELATED PEPTIDE

- PTHrP is a paracrine factor secreted by many tissues; e.g., lung, mammary tissue, placenta.
- It may have a role in fetal development. In postnatal life its role is unclear.
- The majority of humoral hypercalcemias of malignancy are due to overexpression of PTHrP.
- PTHrP has a strong structural homology to PTH and binds with equal affinity to the PTH receptor

BONE REMODELING

- Bone is undergoing continual remodeling throughout life, although the turnover is faster in younger individuals. As many as 300,000 bone-remodeling sites are active in a normal person.
- Peak bone mass is generally obtained in early adulthood. It then tends to decline (at least in sedentary individuals) and accelerates in women in the perimenopausal period.
- Remodeling occurs more in cancellous (trabecular or low-density) bone than in cortical (compact or high-density) bone.
- Remodeling occurs along force lines generated by mechanical stresses. The osteocytes are mechano-receptors that pick up vibrations and relay this information to the bone surface and osteoblasts, which then initiate the remodeling process. For example, a bowing deformity initiates new bone deposition on the concave side of the stressed bone, thus increasing overall strength.
- The remodeling sites are depicted in Figure X-7-5.

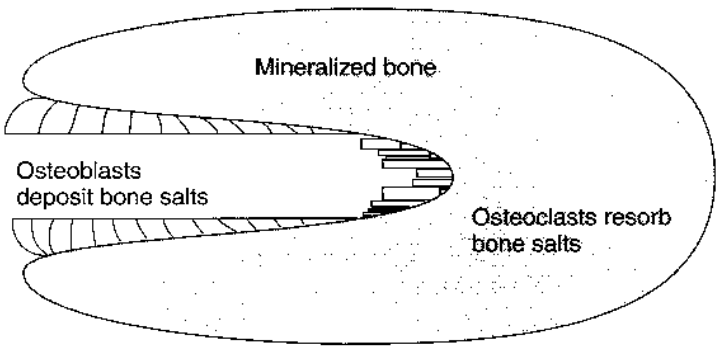


Figure X-7-5. Bone Remodeling

Active remodeling sites can be envisioned as advancing columns of bone-resorbing osteoclasts, followed by rows of osteoblasts, which lay bone down again. Upon mineralization, these remodeling sites become the basic structural units of bone (i.e., the osteons or Haversian systems). When surrounded by mineralized bone, the osteoblasts differentiate into osteocytes.

Weight-Bearing Stress

Though poorly understood, weight-bearing mechanical stress increases the mineralization of bone.

The absence of weight-bearing stress (being sedentary, bedridden, or weightless) promotes the demineralization of bone. Under these conditions, the following occurs:

- Plasma Ca^{2+} tends to be in the upper region of normal.
- Plasma PTH decreases.
- Urinary calcium increases.

Indices

Indices can be utilized to detect excess bone demineralization and remodeling:

- Increased serum osteocalcin and alkaline phosphatase are associated with osteoblastic activity.
- Increased urinary excretion of hydroxyproline is a breakdown product of collagen

ROLE OF VITAMIN D_3 (CHOLECALCIFEROL) IN CALCIUM HOMEOSTASIS

Sources of Cholecalciferol and Synthesis of 1,25 di-OH D_3

Vitamin D_2 is a vitamin but can functionally be considered a prohormone. It is a normal dietary component. A slightly different form, vitamin D_3, is synthesized in the skin. Its active form (1,25 di-OH D_3) is a hormone secreted by cells of the kidney's proximal tubule. The synthesis of 1,25 di-OH D_3 is outlined in Figure X-7-6.

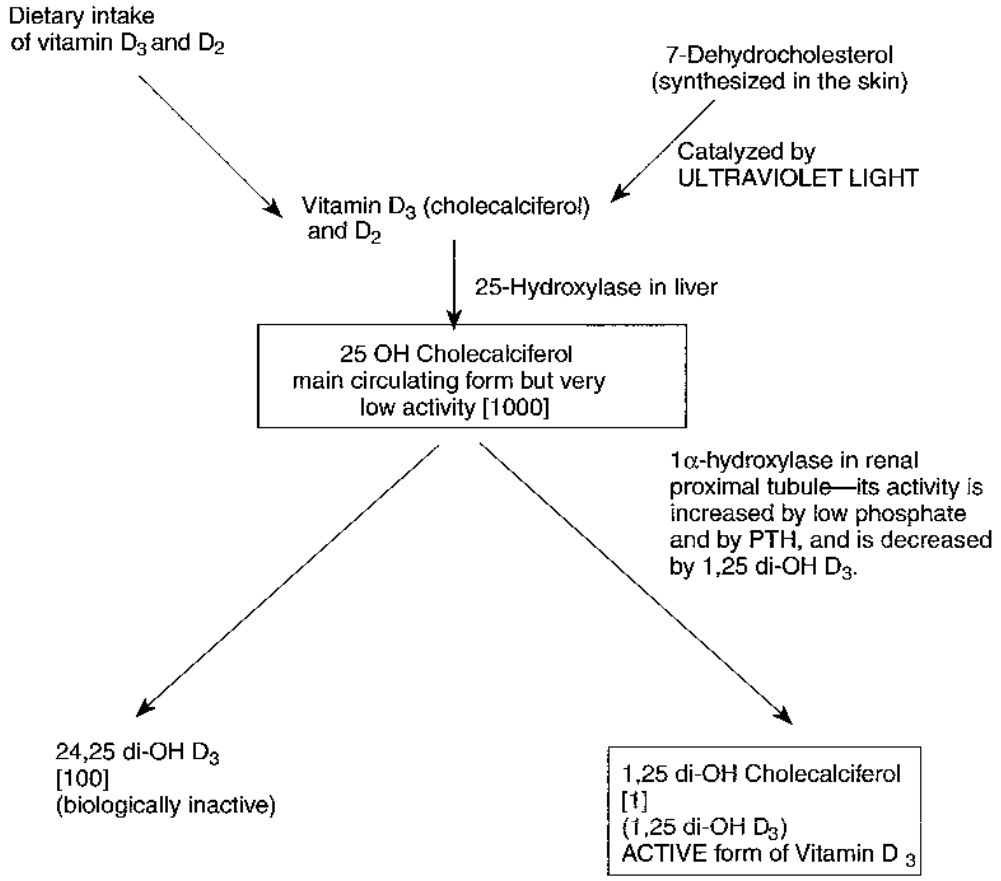


Figure X-7-6. Vitamin D Metabolism

The synthesis of 1,25 di-OH D_3 occurs sequentially in the skin → liver → kidney. The relative numbers of molecules of each of the hydroxylated forms of D_3 present in the blood of a normal person are given in brackets. After its conversion to the 25 OH form in the liver, it can be stored in fat tissue. The serum levels of 25 OH vitamin D represent the best measure of the body stores of vitamin D when a deficiency is suspected. Most of the 25 OH form, which is the immediate precursor of 1,25 di-OH D_3, is converted to the inactive metabolite, 24,25 di-OH D_3. Ultraviolet (UV) light also evokes skin tanning, decreasing the penetration of UV light, and thus decreases the subsequent formation of D_3. This mechanism may prevent overproduction of D_3 in individuals exposed to large amounts of sunlight.

Actions of 1,25 di-OH D_3

Under normal conditions, vitamin D acts to raise plasma Ca^{2+} and phosphate. Thus, vitamin D promotes bone deposition. This is accomplished by:

- 1,25 di-OH D_3 increases the absorption of Ca^{2+} and phosphate by the intestinal mucosa by increasing the production of Ca^{2+}-binding proteins. The details of this process are poorly understood.
- The resulting high concentrations of Ca^{2+} and phosphate in the extracellular fluid exceed the solubility product, and precipitation of bone salts into bone matrix occurs.
- 1,25 di-OH D_3 increases the reabsorption of Ca^{2+} by renal distal tubule.

At abnormally high activity levels 1,25 di-OH D_3 increases bone resorption and release of Ca^{2+} and phosphate from bone. Receptors for 1,25 di-OH D_3 are on the nuclear membranes of osteoblasts. Through communication from osteoblasts, activated osteoclasts carry out the bone resorption. 1,25 di-OH D_3 requires the concurrent presence of PTH for its bone-resorbing action.

Figure X-7-7 provides an overview of regulation of calcium and phosphate by parathyroid hormone and vitamin D. Calcitonin effects are not provided in detail.

Summary

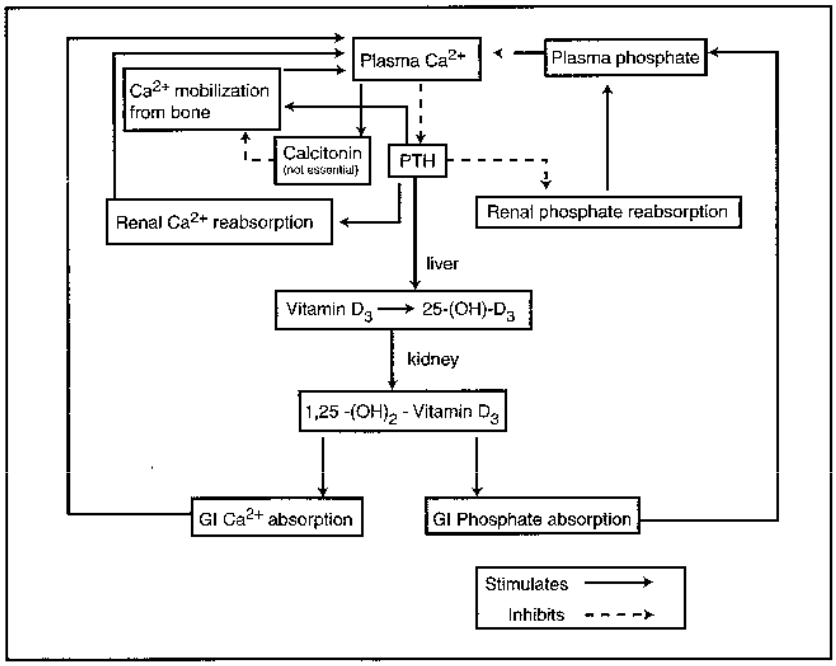


Figure X-7-7. Regulation of Calcium and Phosphate

DISORDERS IN CALCIUM AND PHOSPHATE METABOLISM

Hypercalcemia

Hypercalcemia of primary hyperparathyroidism

- Initiating factor is primary hypersecretion of PTH
- Consequences include increased plasma calcium, decreased plasma phosphate, polyuria and calciuria and decreased bone mass
- 80% due to a single parathyroid adenoma
- 15% due to primary hyperplasia as in MEN 1 or MEN 2A
- Parathyroid carcinoma rare
- Ectopic hormonal hypercalcemia usually PTHrP, e.g., in pheochromocytoma
- Most patients asymptomatic
- Symptoms include lethargy, fatigue, depression, neuromuscular weakness, difficulty in concentrating

- Increased plasma alkaline phosphatase, osteocalcin and increased excretion of cAMP (second messenger for PTH in the kidney), and hydroxyproline
- Symptoms usually develop slowly; rarely is there severe dehydration and coma, the so-called "hypercalcemic parathyroid crisis"
- Bone manifestation is osteitis fibrosa cystica in which there are increased osteoclasts in scalloped areas of the surface bone and replacement of marrow elements with fibrous tissue. Increased alkaline phosphatase is due to high bone turnover.
- Bone loss is a consequence of all hypercalcemic states except milk-alkali syndrome.
- Hypercalcemia decreases QT interval and in some cases causes cardiac arrhythmias.

Related causes of hypercalcemia

- Lithium shifts the sigmoid Ca/PTH curve to the right. Higher calcium levels are thus needed to suppress PTH. A rare familial defect which reduces the Ca receptor sensitivity in a similar way results in hypercalcemia.
- Sarcidosis and other granulomatous disorders (10%) due to increased activity of vitamin D
- Thyrotoxicosis, milk-alkali syndrome

Differential diagnosis and treatment

- Elevated plasma calcium and PTH normal or elevated; conclusion is primary hyperparathyroidism
- Elevated plasma calcium and decreased PTH; conclusion is something other than primary hyperparathyroidism
- Treatment is usually surgery; i.e., removing the adenoma or with hyperplasia removing most of the parathyroid tissue

Hypocalcemia

Hypocalcemia of primary hypoparathyroidism

- Can be hereditary or acquired gland failure or an acute but reversible dysfunction
- Most common cause was thyroid surgery but now surgery to correct hyperparathyroidism
- The initiating factor is inadequate secretion of PTH by the parathyroid glands.
- The decrease in plasma calcium is accompanied by an increased plasma phosphate. Even though less phosphate is resorbed from bone, plasma phosphate increases because the normal action of PTH is to inhibit phosphate reabsorption and increase excretion by the kidney. Therefore, without PTH, more of the filtered load is reabsorbed.
- Symptoms focus on the hypocalcemic induced increased excitability of motor neurons creating muscular spasms and tetany
- Chvostek's sign is induced by tapping the facial nerve just anterior to the ear lobe.
- Trousseau's sign is elicited by inflating a pressure cuff on the upper arm. A positive response is carpal spasm.
- Hypomagnesemia prevents PTH secretion and induces a temporary hypocalcemia. This condition responds immediately to an infusion of mansesium.

Pseudohypoparathyroidism

- This is a rare familial disorder characterized by target tissue resistance to parathyroid hormone.
- Exhibits same signs and symptoms as primary hypoparathyroidism except PTH elevated
- It is usually accompanied by developmental defects: mental retardation, short and stocky stature, one or more metacarpal or metatarsal bones missing (short 4th or 5th finger).

Additional causes of hypocalcemia

- Acute hypocalcemia can occur even with intact homeostatic mechanisms. Included would be alkalosis via hyperventilation, transfusions of citrated blood, rhabdomyolysis or tumor lysis, and the subsequent hyperphosphatemia
- Hyperphosphatemia of chronic renal failure
- Most other causes involve failures with the vitamin D system
- Congenital absence of parathyroids rare (DiGeorge's syndrome)

Predictive indices for a primary disorder

When plasma calcium and phosphate levels are changing in opposite directions, the cause is usually a primary disorder. An exception may be chronic renal failure. This state is not a primary disorder but is usually associated with hypocalcemia and hyperphosphatemia (hypocalcemic-induced secondary hyperparathyroidism).

Vitamin D Deficiency and Secondary Hyperparathyroidism

- Causes include a diet deficient in vitamin D, inadequate sunlight exposure, malabsorption of vitamin D, enzyme deficiencies in the pathway to activation of vitamin D
- In all cases there is a decrease in plasma calcium, which elicits an increase in PTH secretion and a secondary hyperparathyroidism.
- A similar consequence is the increased demand for calcium as in pregnancy.
- Characterized by increased PTH, decreased plasma calcium, and decreased plasma phosphate. Even though the elevated PTH increases phosphate resorption from bone, PTH also inhibits phosphate reabsorption by the kidney, thereby promoting phosphate excretion and a drop in plasma phosphate.
- Bone mass is lost to maintain plasma calcium.
- Diagnostic would be a low plasma 25(OH) vitamin D.

Excess Vitamin D and Secondary Hypoparathyroidism

- An excessive intake of vitamin D raises plasma calcium, which will elicit a decrease in PTH
- Characterized by decreased PTH, increased plasma calcium, and increased plasma phosphate but normal or decreased phosphate excretion. Because PTH increases the excretion of phosphate by inhibiting reabsorption in the proximal tubule, decreased PTH will cause increased reabsorption of phosphate and drive plasma levels higher.
- Excessive vitamin D promotes bone resorption and bone mass decreases.

Predictive indices for a secondary disorder

When the plasma calcium and phosphate are changing in the same direction, the origin is usually a secondary disorder.

- Secondary hyperparathyroidism: both decrease
- Secondary hypoparathyroidism: both increase

Note also that in either a deficiency or an excess of vitamin D, there is a decrease in bone mass but for completely different reasons.

METABOLIC BONE DISORDERS

Osteoporosis

- Osteoporosis is a loss of bone mass (both mineralization and matrix) with fractures, due to normal age-related changes in bone remodeling as well as additional factors that exaggerate this process.
- If bone mineral density is 2.5 standard deviations below the average, then this equals osteoporosis.
- If bone mineral density is 1 to 2.5 standard deviations below the average, then this equals osteopenia.
- Bone mass reaches a peak subsequent to puberty. Heredity accounts for most of the variation but physical activity, nutrition, and reproductive hormones play a significant role, especially estrogens even in men.
- Secondary osteoporosis can occur in thyrotoxicosis and particularly with elevations in glucocorticoids.
- A mainstay of treatment involves the use of bisphosphonates that are rapidly incorporated into bone and reduce the activity of osteoclasts.

Rickets and Osteomalacia

- Origin is the abnormal mineralization of bone and cartilage
- Rickets is before plate closure, osteomalacia is after plate closure.
- In rickets there is expansion of the epiphyseal plates and the most striking abnormalities are the bowing of the legs and protuberant abdomen.
- In osteomalacia, symptoms are more subtle.
- Most common cause is a vitamin D deficiency but also with dietary deficiencies in calcium and phosphate.
- Rarely, it can be caused by enzyme deficiencies when substrate availability is normal.

Chapter Summary

* Only a percentage of the ingested calcium is absorbed from the small intestine and this percentage is decreased in the elderly.
* It is the ECF free calcium that is the biological active, precisely regulated form.
* Alkalosis decreases the ECF free calcium.
* Bone deposition and resorption depend upon the product of the calcium and phosphate concentrations.
* ECF free calcium is regulated by parathyroid hormone (PTH) and vitamin D (a prohormone).
* PTH raises calcium by fast and slow actions.
* Fast actions of PTH include increased renal distal tubule reabsorption of calcium and decreased proximal tubule reabsorption of phosphate.
* Slow actions of PTH include activating osteoclasts and increasing the actions of vitamin D.
* Bone is constantly being remodeled and mechanical stress increases and bed rest decreases overall bone mass.
* The main circulating form of vitamin D is the 25-OH form, but the active physiologic form is the 1,25 di-OH form.
* The most common cause of hypercalcemia is primary hyperparathyroidism (↑ calcium, ↓ phosphate).
* Hypercalcemia is usually associated with bone loss.
* The most common cause of primary hypoparathyroidism is surgery (↓ calcium, ↑ phosphate).
* Hypocalcemia induces muscular tetany.
* Vitamin D deficiency induces a secondary hyperparathyroidism (↓ calcium, ↓ phosphate) and a decrease in bone mass (rickets, osteomalacia).
* Vitamin D excess induces a secondary hypoparathyroidism (↑ calcium, ↑ phosphate) and the increased activity of vitamin D directly decreases bone mass.
* Chronic renal failure often induces a hyperphosphatemia and a secondary hyperparathyroidism (↓ calcium, ↑ phosphate).
* Osteoporosis is mainly an age-related process in which the bone matrix and mineralization decrease.
* In rickets and osteomalacia there is mainly a decrease in the mineralization of bone.

Thyroid Hormones

In mammals, thyroid hormones are essential for normal growth and maturation. Therefore, thyroid hormones are major anabolic hormones.

Dietary intake, mainly in the form of iodide (I^-) of about 500 μg per day, is typical. To maintain normal thyroid hormone secretion, 150 μg is the minimal intake necessary. I^- is the form absorbed from the small intestine.

ORGANIZATION OF THE THYROID GLAND

- The functional unit is the follicle.
- The lumen is filled with thyroglobulin, to which are covalently bound large numbers of thyroid hormone molecules.
- Surrounding the lumen are the follicle cells, which function to both synthesize and release thyroid hormones.
- These relationships are schematically represented in Figure X-8-1.

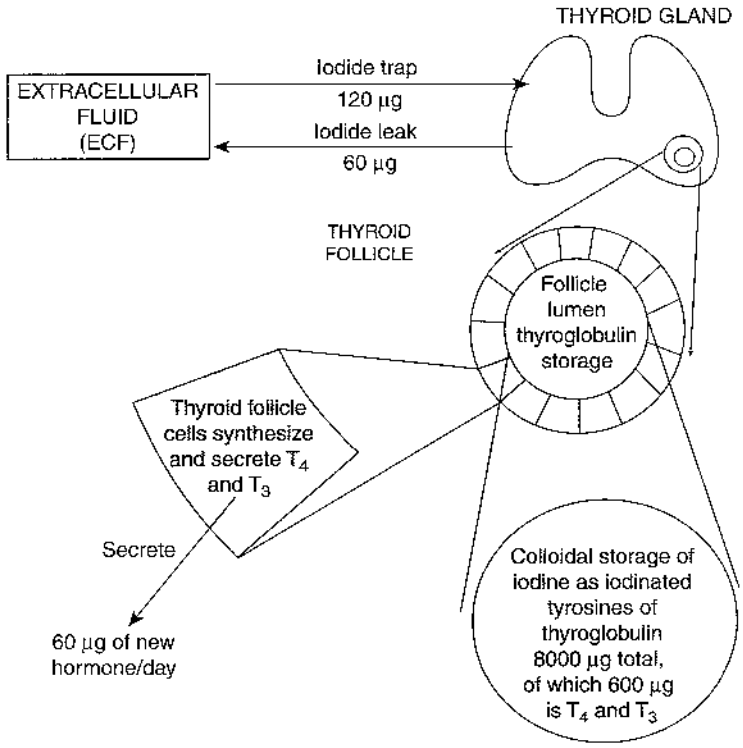


Figure X-8-1. The Thyroid Follicle

SYNTHESIS, STRUCTURE, AND SECRETION OF THYROID HORMONES

Synthesis of Thyroid Hormones

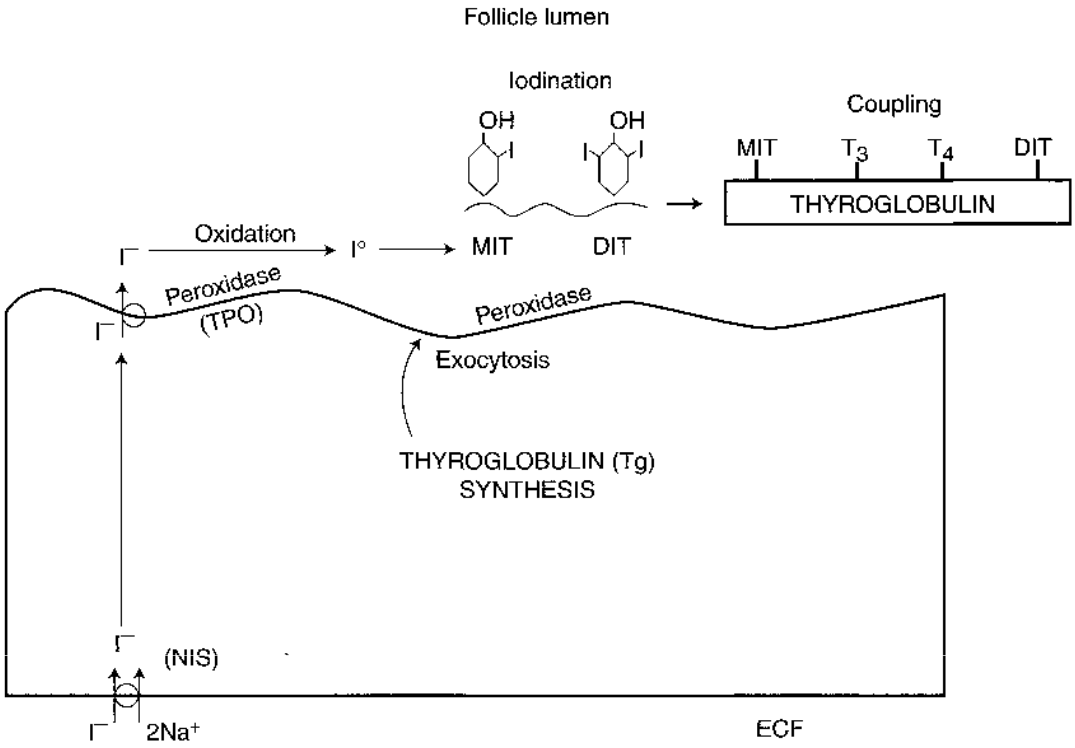


Figure X-8-2. Steps in Thyroid Synthesis

Iodide transport

Iodine uptake is via a sodium/potassium pump powered sodium/iodide symporter on the basal membrane (NIS). This pump can raise the concentration of I^- within the cell to as much as 250 times that of plasma. The pump can be blocked by anions like perchlorate and thiocyanate, which compete with I.

Along the apical membrane, the I^- is transported into the lumen by a sodium-independent transporter referred to as pendrin.

The 24-hour iodine uptake by the thyroid is directly proportional to thyroid function. This is shown in Figure X-8-3.

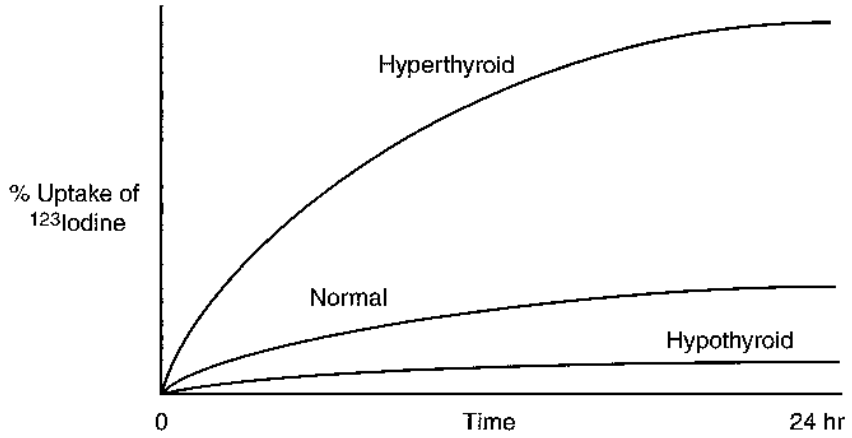


Figure X-8-3. Relationship of Thyroid Function and Iodine Uptake

Thyroglobulin synthesis

A high molecular weight protein (>300,000 daltons) is synthesized in ribosomes, glycosylated in the endoplasmic reticulum, and packaged into vesicles in the Golgi apparatus. The thyroglobin then enters the lumen via exocytosis.

Oxidation of I^- to I°

The enzyme, thyroperoxidase (TPO), which is located at the apical border of the follicle cell, catalyzes oxidation. Peroxidase also catalyzes iodination and coupling.

Iodination

As thyroglobulin is extruded into the follicular lumen, a portion (<20%) of its tyrosine residues are iodinated. The catalyst for this reaction is peroxidase. The initial products of iodination are mono- and diiodotyrosine (MIT and DIT), respectively, with the latter form predominating, except when iodine is scarce.

Large amounts of iodine will inhibit thyroid hormone synthesis by suppressing peroxidase (Wolff-Chaikoff effect). The normal thyroid will eventually escape this suppressive effect of elevated iodine. An abnormally functioning thyroid will often not escape and thyroid hormone synthesis remains depressed.

Coupling

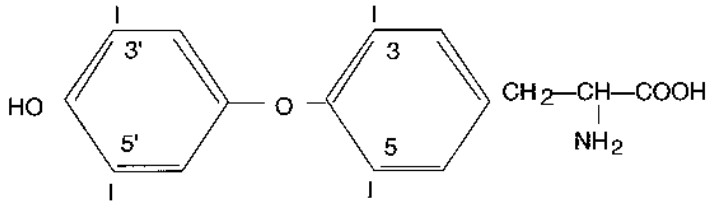
Peroxidase also promotes the coupling of iodinated tyrosine in the thyroglobulin molecule. When two DITs couple, tetraiodothyronine (T_4) is formed. When one DIT and one MIT combine, triiodothyronine (T_3) is formed. When iodine is abundant, mainly T_4 is formed. But when iodine becomes scarce, the production of T_3 increases.

Storage of thyroid hormones

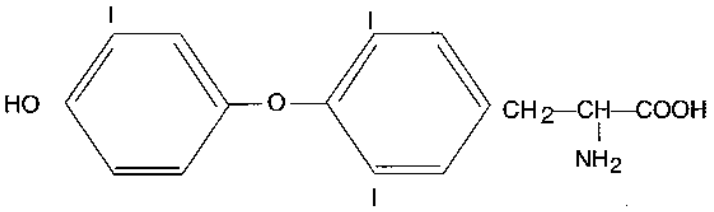
Enough hormone is stored as iodinated thyroglobulin in the follicular colloid to last the body for 2–3 months.

Structure of Thyroid Hormones

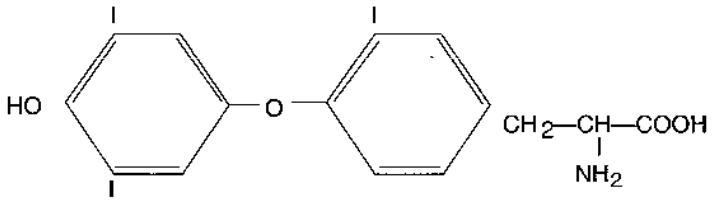
The chemical structures of T_4, T_3, and reverse T_3 (rT_3) are shown in Figure X-8-4. Do no memorize structure; note the number and location of iodines, instead, attached to the tyrosine residues.



Thyroxine (T_4) 3,5,3',5',-tetraiodothyronine



3,5,3'-triiodothyronine (T_3)
- More active form of hormone
- No 5' I



3,3',5'-triiodothyronine (reverse T_3)
- No activity
- no 5 I

Figure X-8-4. Active and Inactive Forms of Thyroid Hormones

Secretion of Thyroid Hormone

Figure X-8-5 illustrates the main steps in thyroglobulin degradation and the release of thyroid hormones.

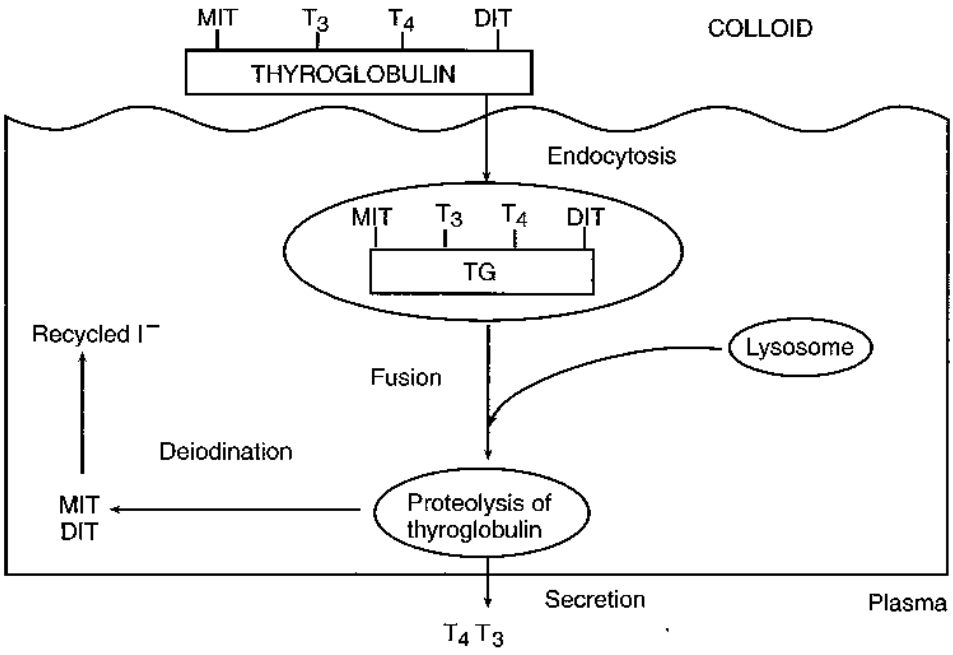


Figure X-8-5. Secretion of Thyroid Hormone

Endocytosis: Pieces of the follicular colloid are taken back into the follicle by endocytosis.

Fusion: The endocytosed material fuses with lysosomes, which transport it toward the basal surface of the cell.

Proteolysis of thyroglobulin: Within the lysosomes, the thyroglobulin is broken into free amino acids, some of which are T4, T3, DIT, and MIT.

Secretion: T4 and T3 are secreted into the blood, the ratio being as high as 20 T4 to 1 T3. The thyroid has the same 5'-monodeiodinase found in many peripheral tissues and in an iodine-deficient state more of the hormone can be released as T3.

Along with thyroid hormones a small amount of thyroglobulin is also released into the circulation. Its release is increased in a number of states including thyroiditis, nodular goiter, and by cancerous thyroid tissue. After the surgical removal of cancerous thyroid tissue, any residual thyroglobulin in the circulation indicates cancerous cells are still present.

Deiodination: A microsomal deiodinase removes the iodine from iodinated tyrosines (DIT and MIT) but not from the iodinated thyronines (T3 and T4). The iodine is then available for resynthesis of hormone. (Individuals with a deficiency of this enzyme are more likely to develop symptoms of iodine deficiency.)

TRANSPORT OF THYROID HORMONES IN BLOOD

There is an equilibrium between bound and free circulating thyroid hormone in the bloodstream. Figure X-8-6 illustrates this equilibrium.

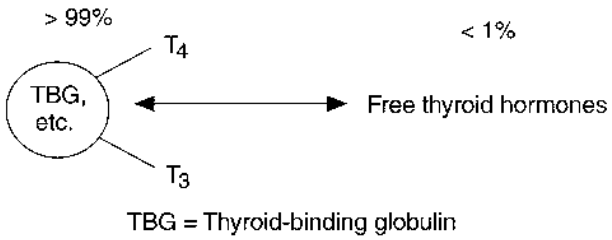


Figure X-8-6. Plasma Transport of Thyroid Hormone

About 70% of the circulating thyroid is bound to thyroglobin (TBG). The remainder of the bound protein is attached to thyroxine-binding prealbumin (transthyretin) and albumin. Large variations in TBG do not normally affect the free form. A rare congenital deficiency or excess of TBG drastically alters the bound fraction but because the free fraction is normal, the individuals are all euthyroid.

Also, T4 has the higher affinity for binding proteins; therefore, it binds more tightly to protein than T3 does, and consequently the half-life of T4 is greater than that of T3. Most circulating thyroid hormone is T4. Normally, there is 50 times more T4 than T3.

- T4 half-life = 6 days
- T3 half-life = 1 day

The amount of circulating thyroid hormone is about 3 times the amount normally secreted by the thyroid gland each day. Thus, circulating protein-bound thyroid hormones act as a significant reserve.

ACTIVATION AND DEGRADATION OF THYROID HORMONES

T_3 and T_4 bind to the same nuclear receptor but T_3 binds with 10 times more affinity than T4. Thus, because it has greater affinity for the receptor, T_3 is the more active form of thyroid hormone. Some also believe that T_4 can be considered simply a circulating prohormone of T_3 and that most of the peripheral activity results from the conversion of T_4 to T_3. However, current evidence still favors some intrinsic biological activity for T_4.

Many target tissues can regulate the conversion of T_4 to either T_3 or rT3, thereby locally controlling hormone activity. In addition even though the thyroid releases some T_3 into the circulation, most of the circulating T_3 is derived from the peripheral conversion of T_4 into T_3 and its release again into the circulation (e.g., liver, kidney, and skeletal muscle). This peripheral conversion of thyroid hormone is represented in Figure X-8-7.

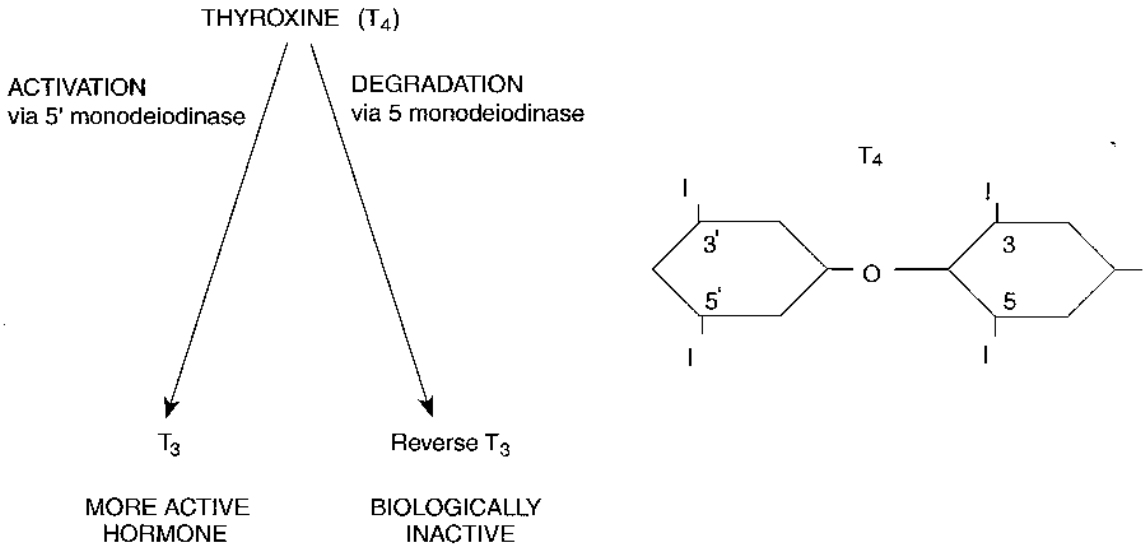


Figure X-8-7. Peripheral Conversion of Thyroid Hormone

Certain clinical states are associated with a reduction in the conversion of T_4 into T_3, often with an enhanced conversion of T_4 into rT3 (low T_3 syndrome). Such states would include fasting, medical and surgical stresses, catabolic diseases, and even excess secretion of cortisol could be included here. The result is a reduction in metabolic rate and a conservation of energy resources. In the early stages, the circulating T_4 is normal but in many cases as the metabolic problem or stress becomes more severe, T_4 can fall as well.

PHYSIOLOGIC ACTIONS OF THYROID HORMONES

In many tissues, thyroid hormones are not the prime indicators or the major inhibitors of specific cellular processes. Rather, a multitude of processes function properly only when optimal amounts of thyroid hormones are present. This underscores the permissive nature of thyroid hormones.

Metabolic Rate

Thyroid hormones increase metabolic rate, as evidenced by increased O_2 consumption and heat production. Thyroid hormones increase the activity of the membrane-bound Na/K-ATPase in many tissues, and it can be argued that it is the increased pumping of Na^+ that accounts for most of the increase in metabolic rate. The increase in metabolic rate produced by a single dose of T_4 occurs only after a latency of several hours but may last 6 days or more. Thyroid hormones do not directly affect the metabolic rate of nervous tissue, uterus, or testes. However, thyroid hormones are absolutely necessary for normal brain maturation and essential for normal menstrual cycles. Hypothyroidism leads to menstral irregularities (menorrhagia) and infertility (anovulatory cycles).

Growth and Maturation (T_4 and T_3 Anabolic Hormones)

Fetal growth rates appear normal in the absence of thyroid hormone production (i.e., if the fetus is hypothyroid). However, without adequate thyroid hormones during the perinatal period, abnormalities rapidly develop in nervous system maturation.

- Synapses develop abnormally and there is decreased dendritic branching and myelination. These abnormalities lead to mental retardation.
- These neural changes are irreversible and lead to cretinism unless replacement therapy is started soon after birth.

Lipid Metabolism

Thyroid hormone accelerates cholesterol clearance from the plasma. Thyroid hormones are required for conversion of carotene to vitamin A, and, as a consequence, hypothyroid individuals can suffer from night blindness and yellowing of the skin.

CHO Metabolism

Thyroid hormone increases the rate of glucose absorption from the small intestine.

Cardiovascular Effects

Thyroid hormones have positive inotropic and chronotropic effects on the heart. The increased contractility is partly direct and partly indirect: they increase the number and affinity of β-adrenergic receptors in the heart, thereby increasing the sensitivity to catecholamines. Acting on the SA node they directly increase heart rate.

Cardiac output is increased, and both heart rate and stroke volume are elevated. Systolic pressure increases are due to increased stroke volume, and diastolic pressure decreases are due to decreased peripheral resistance.

Thyroid hormones in the normal range are required for optimum cardiac performance.

Additional Effects

Thyroid hormones maintain the ventilatory response to hypoxia, increase erythropoietin, and increase gut motility and bone turnover.

CONTROL OF THYROID HORMONE SECRETION

Feedback Relationships

Figure X-8-8 shows the overall control of thyroid function.

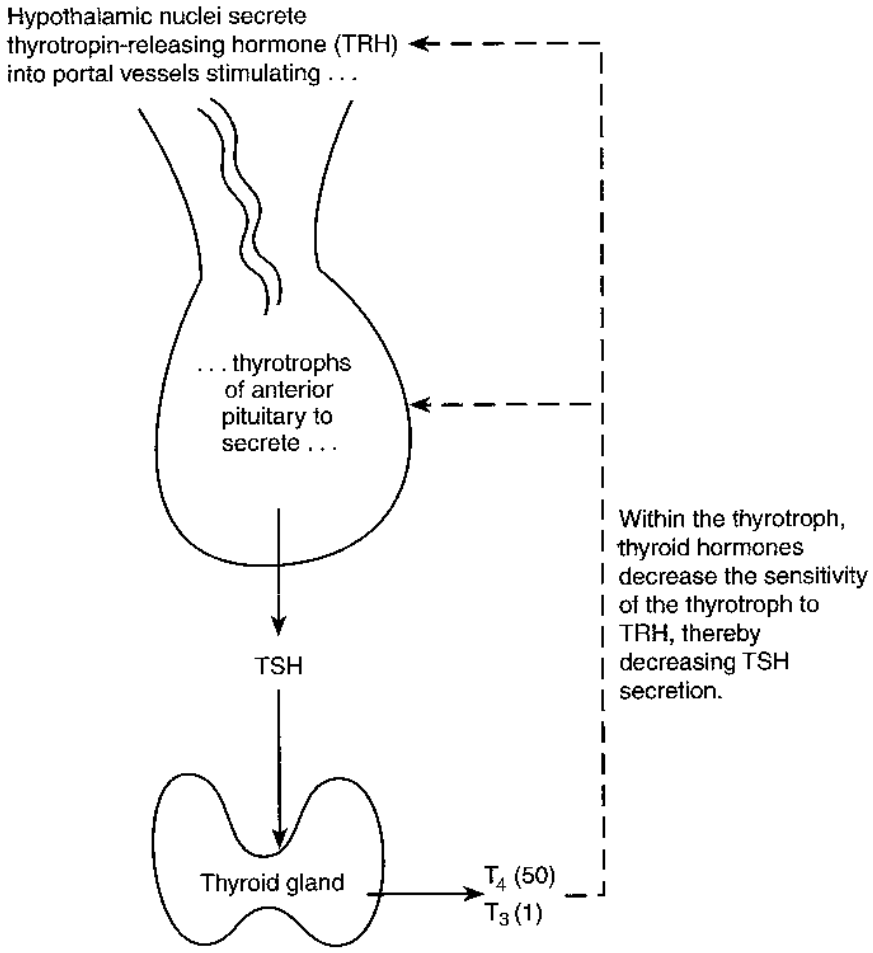


Figure X-8-8. Hypothalamic–Pituitary Control of Thyroid-Hormone Secretion

- TRH provides a constant and necessary stimulus for TSH secretion. In the absence of TRH, the secretion of TSH (and T_4) decreases to very low levels. The target tissue for TSH is the thyroid, where it increases the secretion mainly of T_4.
- Negative feedback of thyroid hormones is exerted mainly at the level of the anterior pituitary gland.
- Because the main circulating form is T_4, it is T_4 that is responsible for most of the negative feedback.
- However, within the thyrotrophs the T_4 is converted to T_3 before it acts to reduce the sensitivity of the thyrotroph to TRH.

- As long as circulating free T_4 remains normal, changes in circulating T_3 have minimal effects on TSH secretion. However, TSH secretion increases if there is a significant drop in circulating free T_4, even in the presence of an increase in circulating T_3.

Overall Effects of Thyrotropin (TSH) on the Thyroid

Rapidly induced TSH effects

TSH tends to rapidly increase (within minutes or an hour) all steps in the synthesis and degradation of thyroid hormones, including:

- Iodide trapping
- Thyroglobulin synthesis and exocytosis into the follicular lumen
- Pinocytotic reuptake of iodinated thyroglobulin back into the thyroid follicular cell
- Secretion of T4 into the blood

Slowly induced TSH effects

Changes that occur more slowly (hours or days) in response to TSH include:

- Increased blood flow to the thyroid gland
- Increased hypertrophy or hyperplasia of the thyroid cells, which initially leads to increased size of the gland or goiter

TESTS OF THYROID FUNCTION

- Determining the serum TSH is the first step in evaluating thyroid function.
- Secondly, free T4 (FT4) measurements are now readily available and would confirm an initial conclusion based on the TSH measurement. An alternative test would be an index of the free T4 via resin uptake.
- Thirdly, a TRH stimulation is not usually necessary, but would differentiate secondary from tertiary hypofunction.
- Autoimmune thyroid disease is easily detected by measuring circulating antibodies. Most notably are the TPO antibodies, which are elevated in Hashimoto's thyroiditis (hypothyroidism) and Grave's disease (hyperthyroidism).
- Additional antibodies are those against thyroglobulin and the TSI antibodies that stimulate the TSH receptor in Grave's disease.
- Uptake of iodine isotopes by the thyroid allows thyroid imaging and quantitation of tracer uptake.
- Subacute thyroiditis: overall a below-normal uptake of isotope
- Grave's disease: increased tracer uptake that is distributed evenly throughout the enlarged gland
- Toxic adenomas: local areas of increased uptake with below-normal uptake in the remainder of the gland
- Toxic multinodular goiter: enlarged gland that often has an abnormal architecture and with multiple areas of high and low uptake.

PATHOLOGIC CHANGES IN THYROID HORMONE SECRETION

Table X-8-1. Changes in Feedback Relationships in Several Disorders

	T_4	TSH	TRH
Primary hypothyroidism	↓	↑	↑
Pituitary hypothyroidism (secondary)	↓	↓	↑
Hypothalamic hypothyroidism (tertiary)	↓	↓	↓
Pituitary hyperthyroidism (secondary)	↑	↑	↓
Grave's disease (autoimmune)	↑	↓	↓

A goiter can develop in all of the disorders shown in the preceding table except secondary and tertiary hypothyroidism.

Thyroidal Response to Low Intake of Iodine

In most cases, if iodine is deficient in the diet but not absent, the individual will remain euthyroid but will develop a goiter. The changes are shown in Figure X-8-9. The adaptive sequence occurs when dietary intake of iodine is deficient. The sequence of events begins with 1 (decreased secretion of T_4) and proceeds through 4, the development of a goiter.

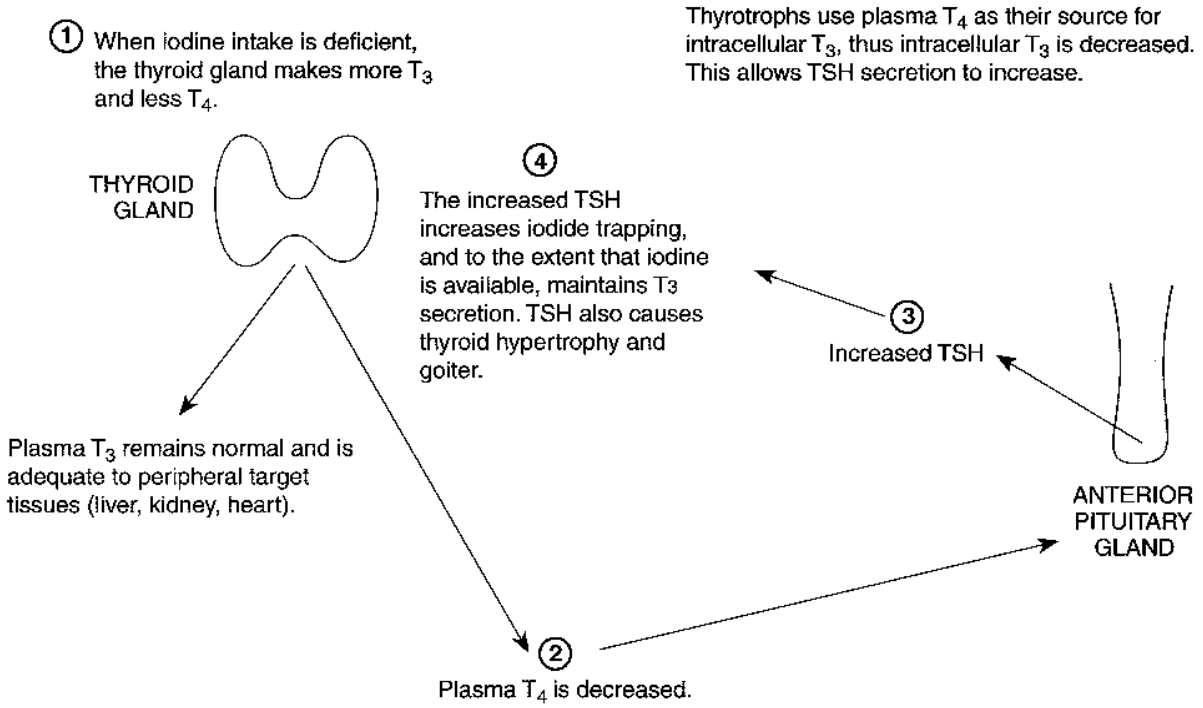


Figure X-8-9. Iodine Deficiency

Primary Hypothyroidism

Primary changes and clinical presentation

- Most common cause is Hashimoto's thyroiditis, an autoimmune destruction of the thyroid with lymphocytic infiltration; ↑ TPO antibodies; early stages have a diffusely enlarged thyroid progressing in the later stages to a smaller atrophic and fibrotic gland.
- ↑ TSH, ↓ FT_4; in subclinical hypothyroidism the TSH is on the high side of normal and the FT_4 is on the low side of normal.
- Decreased basal metabolic rate and oxygen consumption
- Plasma cholesterol and other blood lipids tend to be elevated.
- Increased TRH drives a hyperprolactinemia. In women it may result in amenorrhea with galactorrhea; more often anovulatory cycles with menorrhagia. In men infertility and gynecomastia.
- Decreased GFR and an inability to excrete a water load, which may lead to hyponatremia.
- Inability to convert carotene to vitamin A may cause yellowing of the skin and night blindness.
- Slow thinking and lethargy; some patients have severe mental symptoms, dementia, or psychosis ("myxedema madness")
- Decreased food intake but individuals tend to be overweight
- Deep tendon reflexes with slow relaxation phase
- In the early stages a decreased cardiac performance due to decreased loading conditions. In the later stages cardiac features suggestive of cardiomyopathy

- Anemia, constipation, hoarseness in speech, and the skin is dry and cool
- A decreased ventilatory drive to hypercapnia and hypoxia
- Accumulation of subcutaneous mucopolysaccharides that give rise to a nonpitting edema (myxedema)
- Myxedema coma is the end stage of untreated hypothyroidism. The major features are hypoventilation, fluid and electrolyte imbalances, and hypothermia and ultimately shock and death.

Cretinism

- Untreated postnatal hypothyroidism results in cretinism, a form of dwarfism with mental retardation.
- Individuals often appear normal following delivery but may display some respiratory difficulty, jaundice, feeding problems, and hypotonia.
- Abnormalities rapidly develop in nervous system maturation, which are irreversible and result in mental retardation.
- Prepubertal growth, including bone ossification, is retarded in the absence of thyroid hormones. A stippled epiphysis is a sign of hypothyroidism in children.
- There is no evidence that thyroid hormones act directly on growth or bone formation. Rather, thyroid hormone appears to be permissive or act synergistically with growth hormone or growth factors acting directly on bone. Thyroid hormone is required for normal synthesis and secretion of growth hormone.
- Acquired hypothyroidism during childhood results in dwarfism but there is no mental retardation.
- At puberty, increased androgen secretion drives an increased growth hormone secretion. This will not occur with depressed levels of thyroid hormones.

Additional causes of hypothyroidism

- Secondary generally associated with panhypopituitarism
- Secondary or tertiary characterized by ↓ TSH and ↓ FT_4
- The preceding could be separated by a TRH stimulation test.
- Severe iodine deficiency (not in the United States)
- Drug induced, e.g. lithium
- Failure to escape from the Wolff-Chaikoff effect following excessive iodine intake
- Rarely there can be resistance to thyroid hormone

Treatment

- Replacement doses of T_4. The goal is to give enough T_4 to normalize serum TSH.
- Because metabolism of T_4 decreases and the plasma half-life increases with age, higher doses of T_4 are required in younger individuals.
- Overall levels of TSH must be checked on occasion to make sure of the proper dosage of T_4.
- In women beyond menopause, overdosing with T_4 can contribute to the development of osteoporosis.

Primary Hyperthyroidism (Grave's Disease)

- Thyrotoxicosis by definition is the clinical syndrome whereby tissues are exposed to high levels of thyroid hormone (= hyperthyroidism)
- The most common cause of thyrotoxicosis is Grave's disease, a primary hyperthyroidism.
- Grave's disease is an autoimmune problem in which one antibody is directed against the thyroid receptor. It is referred to as the thyroid stimulating antibody (TSI or TSH-R).
- In addition TPO antibodies and those against thyroglobulin are also found in Grave's disease.
- ↑ FT4, ↓ TSH; it is the TSI stimulating the TSH receptor on the thyroid that is driving the hyperthyroidism.
- In Grave's disease the thyroid is symmetrically enlarged.
- Additional laboratory findings would be increased radioiodine uptake by the thyroid and decreased serum cholesterol.
- Increased metabolic rate and heat production. Individuals tend to seek a cool environment.
- Cardiac output, contractility, and heart rate are increased with possibly palpitations and arrhythmias (increased β-adrenergic stimulation)
- Many symptoms suggest a state of excess catecholamines but circulating catecholamines are usually normal.
- Weight loss with increased food intake, protein wasting, and muscle weakness.
- Tremor, nervousness, and excessive sweating.
- The wide-eyed stare (exophthalmos) in patients with Grave's is caused by an infiltration of orbital soft tissues and extraocular muscles and the resulting edema.
- Untreated hyperthyroidism may decompensate into a condition called "thyroid storm."
- The end-stage of Grave's disease is often a hypothyroidism.

Additional origins of hyperthyroidism (thyrotoxicosis)

- Autonomously functioning thyroid adenoma
- Toxic multinodular goiter
- Subacute and silent thyroiditis
- TSH-secreting pituitary adenoma (secondary hyperthyroidism)

Goiter

- A goiter is simply an enlarged thyroid and does not designate functional status. A goiter can be present in hypo-, hyper-, and euthyroid states. There is no correlation between thyroid size and function.
- A generalized enlargement of the thyroid is considered a "diffuse goiter."
- Diffuse enlargement often results from prolonged stimulation by TSH or TSH-like factor; e.g., Hashimoto's thyroiditis, Grave's disease, diet deficient in iodine
- An irregular or lumpy enlargement of the thyroid is considered a "nodular goiter."
- With time, excessive stimulation by TSH can result in a multinodular goiter e.g. iodine deficiency initially produces a diffuse nontoxic goiter. Long term however, focal hyperplasia with necrosis and hemorrhage results in the formation of nodules. Nodules vary from "hot nodules" that can trap iodine to "cold nodules " that cannot trap iodine.

Chapter Summary

* Thyroid hormones are anabolic and are required for normal growth and maturation.
* Thyroid follicles store several months supply of thyroid hormone.
* The thyroid synthesizes and releases mainly T_4 but on an iodine-deficient diet, the production and release of T_3, a more active form of the hormone, increases.
* T_4 may be considered a prohormone. Most of the activity is due to the peripheral conversion of T_4 into T_3.
* Thyroid hormones increase metabolic rate, conversion of carotene to vitamin A and increase cardiac performance.
* Thyroid hormone is required for postnatal brain maturation. Cretinism is a form of dwarfism with mental retardation.
* Circulating T_4 creates most of the negative feedback to the anterior pituitary but the T_4 entering the thyrotropes must be converted into T_3 before it creates negative feedback.
* Tests of thyroid function focus on the circulating TSH and FT_4.
* Primary hypothyroidism is mainly due to Hashimoto's thyroiditis and results in decreased FT_4 and increased TSH.
* Primary hyperthyroidism is mainly due to Grave's disease. The autoimmune factor stimulating the thyroid increases FT_4 and decreases TSH.
* A goiter, which can be described as diffuse or nodular, is simply an enlarged thyroid and does not designate functional status.
* Individuals on an iodine-deficient diet develop large goiters but they are usually euthyroid.

Growth, Growth Hormone, and Puberty

GROWTH

Intrauterine Growth

- Genetic factors determine early growth; maternal factors more important later in gestation
- Anabolic hormones except thyroid hormone required for normal development
- Important roles for growth hormone, IGF-II (early in gestation), IGF-I (later in gestation) and insulin
- Infants of diabetic mothers have increased insulin levels and are large.
- Smoking decreases vascularity of the placenta and decreases birth weight.
- Poor maternal nutrition leading cause of low birth weight worldwide.

Postnatal Growth

- Although fetal hypothyroidism does not decrease birth weight, hypothyroidism following delivery causes irreversible abnormalities in nervous system maturation, which in turn lead to mental retardation (cretinism).
- Growth hormone, insulin, and thyroid hormone play major roles. Acquired hypothyroidism later in childhood will slow growth and reduce bone advancement more than growth hormone deficiency, but will not cause mental retardation.
- Replacement of hormone deficiencies creates a period of catch-up growth, but it is soon replaced with a normal growth rate.
- There is no major role for gonadal sex steroids on prepubertal growth or for glucocorticoids but glucocorticoid excess will slow growth.
- Hypersecretion of growth hormone pre-puberty (pituitary adenoma) results in giantism. It also delays pubertal changes, and the subsequent hypogonadism contributes to the giantism.

Prepubertal Growth Hormone Deficiency

- Congenital deficiency is associated with decreased birth length.
- Idiopathetic deficiency is due to decreased growth hormone-releasing hormone (GHRH).
- Classic congenital deficiency creates short stature, delayed skeletal maturation, proneness to episodes of hypoglycemia, and a chubby, immature facial appearance.
- Acquired deficiency may be due to a hypothalamic–pituitary tumor.
- Growth hormone deficiency leads to dwarfism.
- Tissue resistance to growth hormone ($\uparrow$ growth hormone, $\downarrow$ IGF-I) results in Laron syndrome (Laron dwarfism).

- Replacement therapy is available for both of the preceding.
- Stimulation test is an insulin-induced hypoglycemia or an arginine infusion.
- Growth hormone deficiency following puberty is not a major problem.

GENERAL FEATURES OF THE GROWTH HORMONE SYSTEM

Growth hormone is a major anabolic growth-promoting hormone and a stress hormone. As stated earlier, all anabolic hormones (i.e., growth hormone, insulin, thyroid hormones, and androgens) are required for normal growth. The major stress and anabolic actions of growth hormone are shown in Figure X-9-1. This figure shows that most of the direct actions of growth hormone are consistent with its actions as a stress hormone. A direct anabolic action is the promotion of amino acid entry into cells, thus making them more available for protein synthesis. However, most of the anabolic actions of growth hormone are indirect via the production of growth factors.

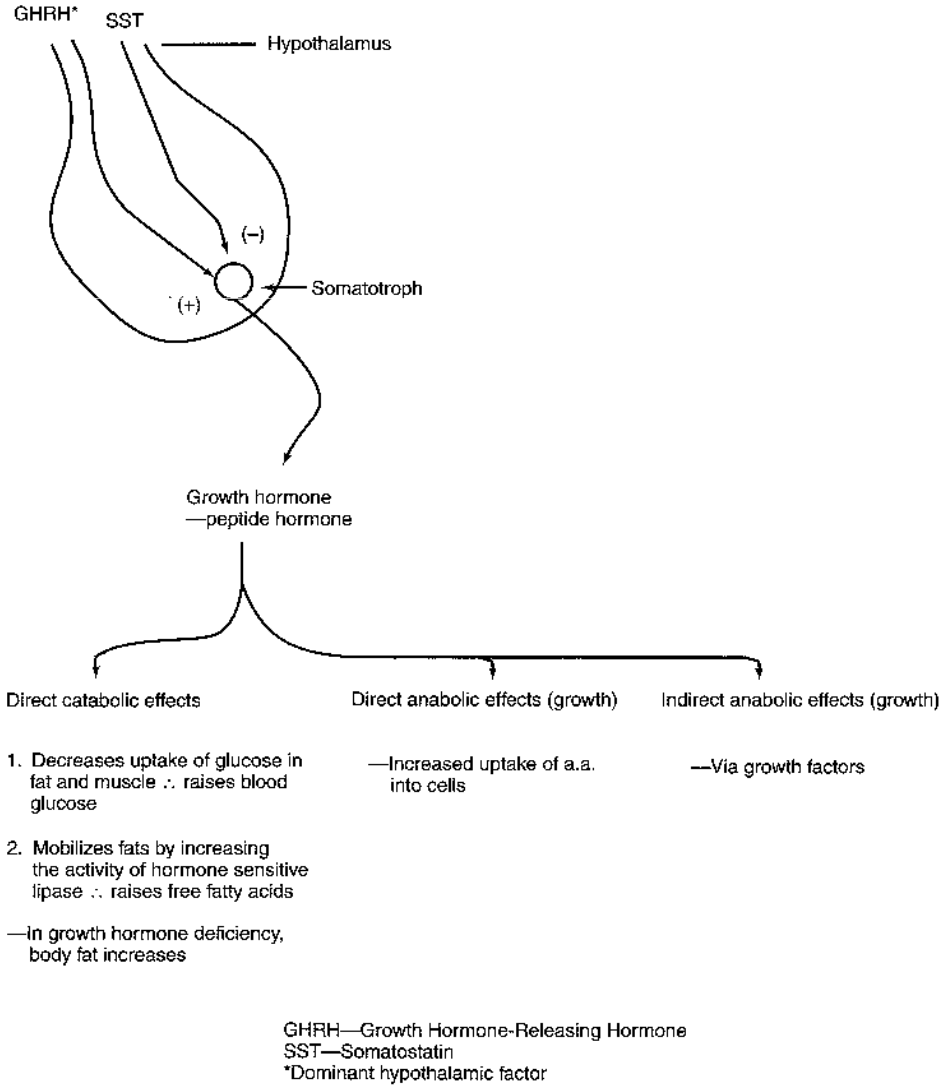


Figure X-9-1. Overview of Growth Hormone

INDIRECT ANABOLIC ACTIONS OF GROWTH HORMONE

Most of the anabolic actions of growth hormone are an indirect result of increased production of growth factors, which are called somatomedins, or insulin-like growth factors (IGFs). A major growth factor is somatomedin C, also called IGF-I.

The steps in the production and release of IGF-I are shown in Figure X-9-2.

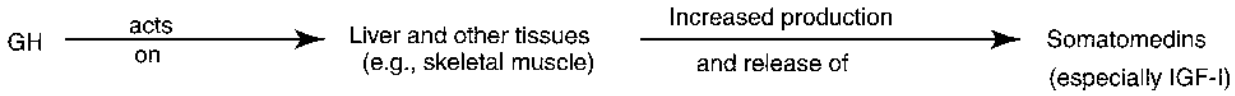


Figure X-9-2. IGF-Mediated Effects of Growth Hormone

Specific Properties of the IGFs

IGF-I is a major anabolic growth factor. It has the following characteristics:

- Circulates peptide growth factor similar in structure to proinsulin and has some insulin-like activity
- Circulates in the blood tightly bound to a large protein, whose production is also dependent on growth hormone. Being bound to a protein, the plasma half-life is very long (20 hours).

Because it has a long half-life, plasma IGF-I serves as a reflection of 24-hour growth hormone secretion. Growth hormone secretion is difficult to measure directly because it is secreted in pulses and mainly at night.

The major known anabolic effect of IGF-I is that it increases the synthesis of cartilage (chondrogenesis) in the epiphyseal plates of long bones, thereby increasing bone length.

It is also hypothesized that circulating IGFs increase lean body mass. The decreased lean body mass of aging may, in part, be due to the concomitant decrease in IGFs. IGFs also decrease in catabolic states, especially protein-calorie malnutrition.

IGF-II is another somatomedin, the importance of which is not well understood but may have a role in fetal development.

CONTROL OF GROWTH HORMONE (GH) SECRETION

- GH secretion is pulsatile. The secretory pulses are much more likely to occur during the night in stages III and IV (non-REM) of sleep than during the day.
- Secretion of GH requires the presence of normal plasma levels of thyroid hormones. GH secretion is markedly reduced in hypothyroid individuals.
- During the sixth decade of life and later, GH secretion diminishes considerably in both men and women. What initiates this decrease is unknown.

The main acute factors that control the secretion of GH are summarized in Figure X-9-3.

The factors listed on the left inhibit GH secretion, and those on the right promote GH secretion. Each of the inhibitors could act by increasing SST (somatostatin) secretion, decreasing GHRH or both.

Each of the promoters could act by increasing GHRH secretion, decreasing SST secretion, or both.

Notice that most of the factors that regulate GH secretion are identical to those that regulate glucagon (except for those boxed). These factors are consistent with their shared role as stress hormones.

The inhibitory effect of IGF-I represents a negative feedback loop to the hypothalamus.

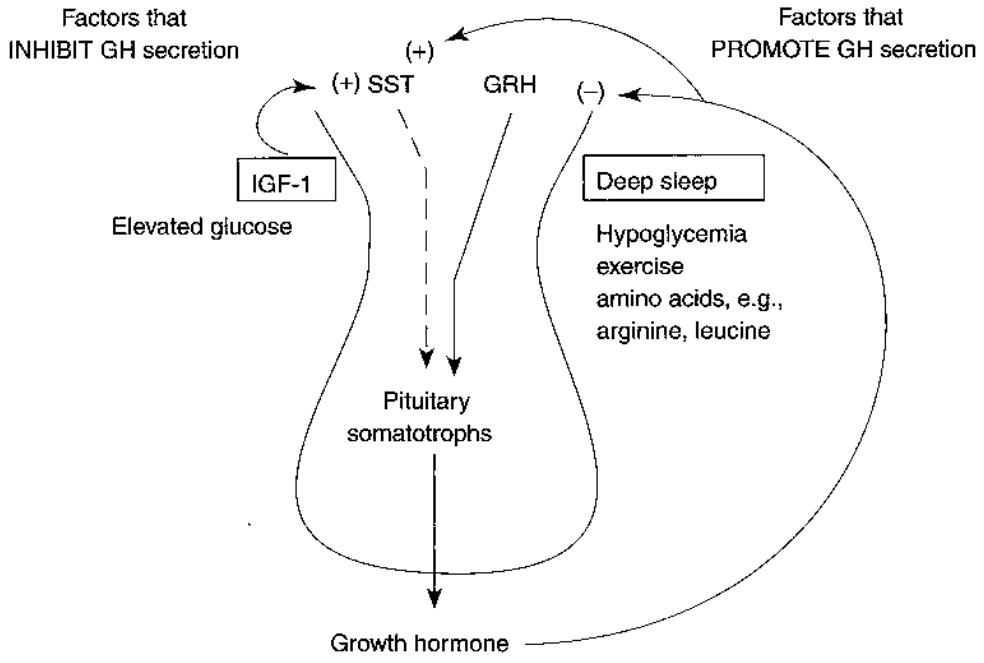


Figure X-9-3. Control of Growth Hormone Secretion

PUBERTY

Reproductive Changes

- Hypothalamic pulse generator increases activity just before physical changes at puberty.
- First noted sign in a female is breast development; first by estrogen (promotes duct growth) then progesterone (promotes development of milk-producing alveolar cells).
- First noted sign in a male is enlargement of the testes. Mainly FSH stimulating seminiferous tubules
- Pubic hair development in males and females is dependent on androgen.

Growth Changes

- During puberty, androgens promote the secretion in the following anabolic sequence:

At puberty, if T4 is normal, ↑ androgens drive ↑ growth hormone, which drives ↑ IGF-I.

- IGF-I is the major stimulus for cell division of the cartilage-synthesizing cells located in the epiphyseal plates of long bones.
- In males, the increased androgen arises from the testes (testosterone); in females, from the adrenals (adrenarche).
- Near the end of puberty, androgens promote the mineralization (fusion or closure) of the epiphyseal plates of long bones. Estrogen can also cause plate closure, even in men.
- In females, the growth spurt begins early in puberty and is near completion by menarche.
- In males, the growth spurt develops near the end of puberty.

ACROMEGALY

- It is caused by a post pubertal excessive secretion of growth hormone.
- It is almost always due to macroadenoma (> 1 cm dia) of the anterior pituitary and second in frequency to prolactinomas.
- There is a slow onset of symptoms, and the disease is usually present for 5 to 10 years before diagnosis.
- Ectopic GHRH secretion occurs but is rare.
- Some tumors contain lactotrophs, and elevated prolactin can cause hypogonadism and galactorrhea.
- Increased IGF-I causes most of the deleterious effects of acromegaly but growth hormone excess directly causes the hyperglycemia and insulin resistance.
- There is characteristic proliferation of cartilage, bone and soft tissue, visceral, and cardiomegaly.
- Observable changes include enlargement of the hands and feet (acral parts) and coarsening of the facial features, including downward and forward growth of the mandible. Also, increased hat size.
- Measurement of IGF-I is a useful screening measure and confirms diagnosis with the lack of growth hormone suppression by oral glucose (not somatostatin).

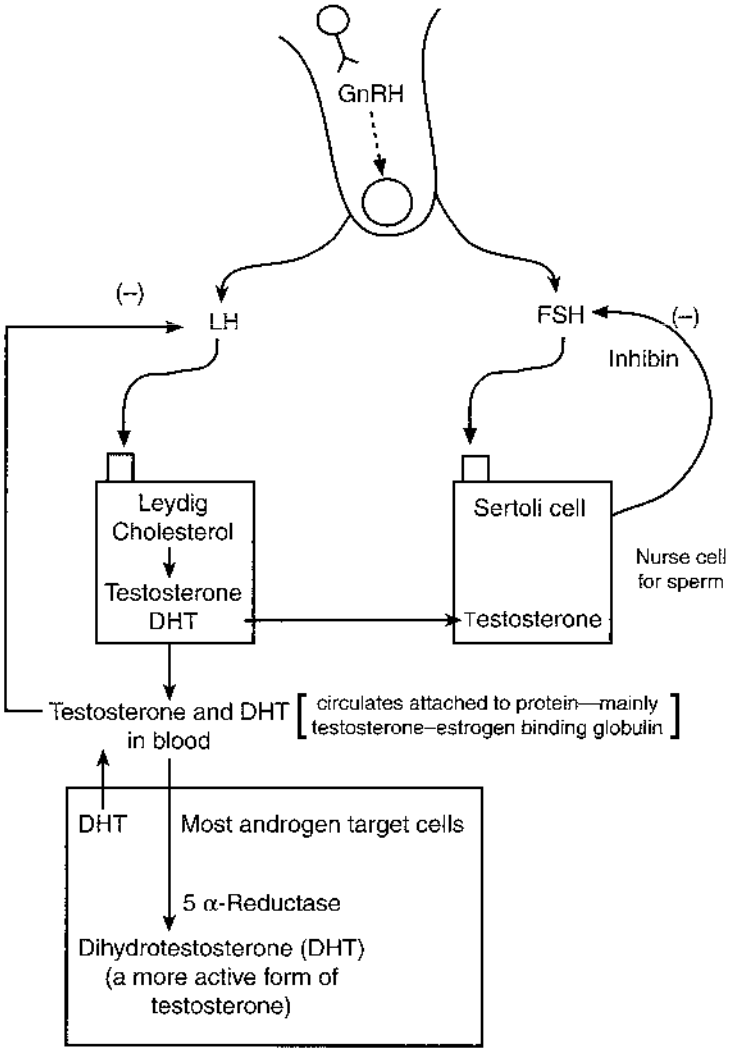
Chapter Summary

* Anabolic hormones except thyroid hormone are required for intrauterine growth.
* Thyroid hormone is required in the perinatal period to prevent mental retardation.
* Sex steroids have no major role prepuberty.
* Excess glucocorticoids slow growth.
* Excess growth hormone accelerates growth, delays pubertal changes, and creates gigantism.
* Prepubertal growth hormone deficiency or tissue resistance to growth hormone (Laron syndrome) leads to dwarfism.
* The most sensitive stimulation test for growth hormone deficiency is insulin-induced hypoglycemia.
* Most of the direct actions of growth hormone are consistent with its actions as a stress hormone; i.e., it decreases the peripheral uptake of glucose and promotes lipolysis.
* Most of the anabolic actions of growth hormone are indirect via growth factors.
* The most important growth factor is IGF-I, which increases the synthesis of cartilage in the epiphyseal plates of long bones.
* Growth hormone secretion is pulsatile and a great deal is released during the night.
* Plasma IGF-I is usually a good index of overall growth hormone secretion.
* The first noted female change at puberty is breast development; in the male it is testes enlargement.
* The increased secretion of growth hormone during puberty is driven by a concurrent increase in androgen secretion.
* The acute factors regulating growth hormone secretion are similar to those regulating glucagon and are consistent with their role as stress hormones.
* Acromegaly is almost always due to pituitary adenoma and most of the deleterious effects due to IGF-I. Noted changes include acral enlargement and coarse facial features. Measurement of IGF-I is useful screening, lack of growth hormone suppression by oral glucose diagnostic.

Male Reproductive System

OVERALL CONTROL OF ADULT MALE HORMONAL SECRETION

The factors involved in the overall control of adult male hormone secretion are summarized in Figure X-10-1.



GnRH—synthesized in preoptic region of hypothalamus and secreted in pulses into hypophyseal portal vessels

- produces pulsatile release of LH and FSH
- pulsatile release of GnRH prevents downregulation of its receptors in anterior pituitary

LH and FSH—produced and secreted by gonadotrophs of anterior pituitary

- are glycoproteins
- TSH and hCG (human chorionic gonadotropin, secreted by placenta, has mainly LH activity) also glycoproteins
- all have α and β subunit. It is the β subunit that provides specificity.

Leydig cell testosterone—some diffuses directly to Sertoli cells, where it is required for Sertoli cell function.

- produces negative feedback for LH

Sertoli cell inhibin—produces negative feedback for FSH

Figure X-10-1. Control of Testes

GnRH is synthesized in the hypothalamus and secreted in pulses into the hypophyseal portal vessels. In the anterior pituitary it stimulates the gonadotrophs, which produce a pulsatile release of LH and FSH.

LH and FSH are glycoproteins. TSH and human chorionic gonadotropin (hCG) are also glycoproteins. All four hormones are composed of an α and a β subunit. The α subunits all have the same structure. It is the β subunit that provides specificity but the dimmer is required for biological activity.

LH receptors are located on the cell membranes of the interstitial **cells of Leydig**. When occupied with LH, these receptors, acting through cAMP/protein kinase as second messenger, stimulate increased conversion of cholesterol to pregnenolone. An increased amount of this hormonal precursor results in increased synthesis and secretion of testosterone. The Leydig cells secrete some dihydrotestosterone, but most of the circulating dihydrotestosterone is derived from the peripheral conversion of testosterone. Small amounts of DHEA and androstenedione (A) are also secreted by the Leydig cells but make up only a tiny fraction of the circulating weak androgens. Much of the testosterone synthesized by the Leydig cells diffuses into adjacent Sertoli cells, where it is required for normal Sertoli cell function.

Circulating testosterone provides a necessary negative feedback signal to both the hypothalamus and the anterior pituitary to regulate LH secretion. Circulating dihydrotestosterone and estrogen may also contribute to the negative feedback.

FSH receptors are located on the plasma membrane of **Sertoli cells**. When occupied with FSH, these receptors acting through a cAMP/protein kinase second messenger increase the production of proteins. Sertoli cells secrete inhibin B. Inhibin acts at the level of the anterior pituitary to provide the negative feedback for FSH. Circulating inhibin B reflects Sertoli cell number and sperm production.

Hormonal Control of Testicular Function

Figure X-10-2 illustrates the source and nature of the hormones controlling testicular function.

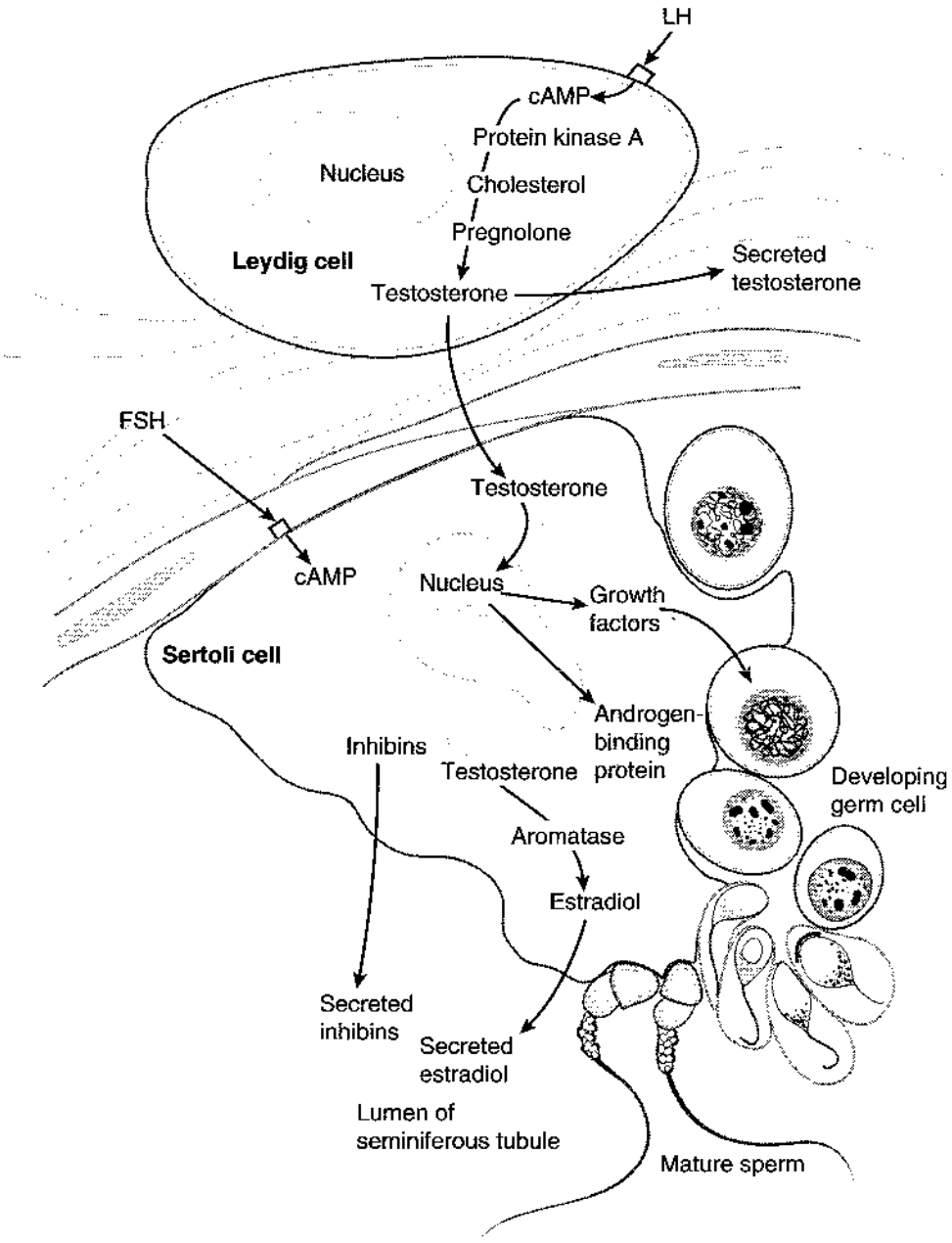


Figure X-10-2. Endocrine Function of Testes

An androgen-binding protein (ABP) synthesized by the Sertoli cells and secreted into the lumen of the seminiferous tubules helps maintain a high local concentration of testosterone to the developing germinal cells during the process of spermatogenesis. This protein is reabsorbed and destroyed by the epididymis and is rarely present in blood. The follicle-stimulating hormone (FSH), in conjunction with testosterone, increases the synthesis of this protein.

Normally, the concentration of testosterone in the testes is 50 times that of the blood.

In a normal male, testosterone acting locally facilitates spermatogenesis. Testosterone receptors are located on the nuclear chromatin of the Sertoli cell. Signals arising from these receptors increase the synthesis of proteins. This increases the movement of nutrient substances from the Sertoli cell to the developing germ cell. The membranes of the Sertoli cells surround the germ cells. Nutrients destined for the germ cells must pass through these membranes.

The actions of FSH, though poorly understood, are essential for the initiation of spermatogenesis. Both FSH and Leydig cell testosterone are required for normal spermatogenesis.

Definitions

Androgen: any steroid that controls the development and maintenance of masculine characteristics

Testosterone: a natural male androgen of testicular origin, controlled by the luteinizing hormone (LH)

Dihydrotestosterone: a more active form of testosterone

Methyl testosterone: a synthetic androgen, which is an anabolic steroid sometimes used by athletes

Adrenal androgens: natural weak androgens (male and female) of adrenal origin, controlled by ACTH

Inhibins: peptide hormones secreted into the blood. They inhibit the secretion of FSH by pituitary gonadotrophs.

Aromatase: an enzyme that stimulates the aromatization of the A-ring of testosterone, converting it into estradiol. The physiologic importance of this conversion is not understood; however, approximately a third of the estradiol in the blood of men arises from Sertoli cells, and the remainder arises from peripheral conversion of testosterone to estradiol by an aromatase present in adipose tissue. One sign of a Sertoli cell tumor is excessive estradiol in the blood of the affected man.

AGE-RELATED CHANGES IN LH AND TESTOSTERONE SECRETION IN THE NORMAL MALE

Figure X-10-3 depicts the relative plasma LH and testosterone concentrations throughout the life of the normal human male. The numbers refer to the descriptions that follow the figure.

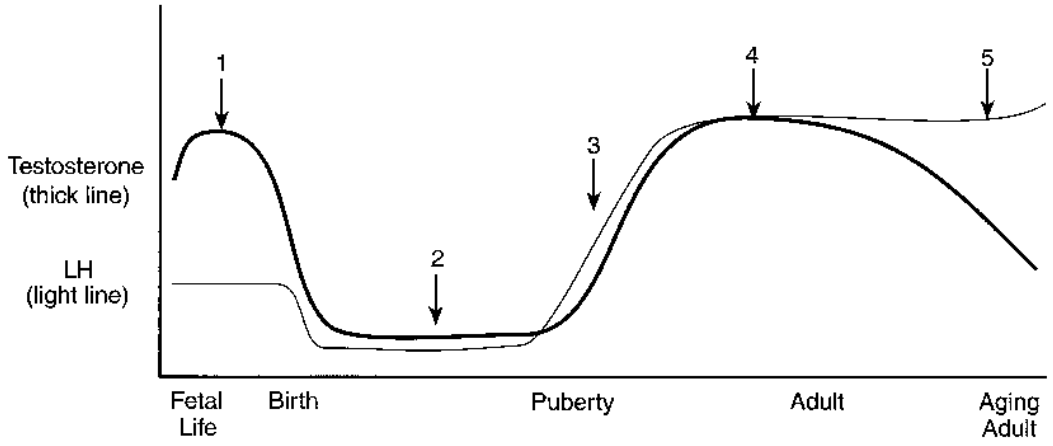


Figure X-10-3. Development and Aging in Male Reproduction

1. Fetal life

The development of male and female internal and external structures depends on the fetal hormonal environment. The Wolffian and Müllerian ducts are initially present in both male and female fetuses. If there is no hormonal input (the situation in the normal female fetus), female internal and female external structures develop (Müllerian ducts develop, Wolffian ducts regress).

Normal male development requires the presence of three hormones: testosterone, dihydrotestosterone, and the Müllerian inhibiting factor (MIH).

1. (hCG) + LH $\rightarrow$ Leydig cells $\rightarrow$ testosterone $\rightarrow$ Wolffian ducts

   5-α-reductase
2. testosterone $\rightarrow$ dihydrotestosterone $\rightarrow$ urogenital sinus and genital organs
3. Sertoli cells $\rightarrow$ MIH $\rightarrow$ absence of female internal structures.

MIH prevents the development of the Müllerian ducts, which would otherwise differentiate into female internal structures. In the absence of MIH, the Müllerian ducts develop. Thus, in addition to normal male structures, a uterus will be present.

- Wolffian ducts differentiate into the majority of male internal structures; namely, epididymis, vasa deferentia, and seminal vesicles. In the absence of testosterone, the Wolffian ducts regress.
- Dihydrotestosterone induces the urogenital sinus and genital tubercle to differentiate into the external scrotum, penis, and prostate gland. In the absence of dihydrotestosterone, female external structures develop.

2. Childhood

Within a few months after birth, LH and testosterone drop to low levels and remain low until puberty. The cause of this prolonged quiescence of reproductive hormone secretion during childhood is not known. Interestingly, LH secretion remains low in spite of low testosterone.

3. Puberty

Near the onset of puberty, the amplitude of the LH pulses becomes greater, driving the mean level of LH higher. Early in puberty, this potentiation of the LH pulses is especially pronounced during sleep. This increased LH stimulates the Leydig cells to again secrete testosterone.

4. Adult

During adulthood, LH secretion drives testosterone secretion. Thus, it is not surprising that the relative levels of the two hormones parallel one another.

5. Aging adult

Testosterone and inhibin secretions decrease with age. Men in their seventies generally secrete only 60–70% as much testosterone as do men in their twenties. Nevertheless, there is no abrupt decrease in testosterone secretion in men that parallels the relatively abrupt decrease in estrogen secretion that women experience at menopause. The loss of feedback will cause an increase in LH and FSH secretion.

Effect on Muscle Mass

The capacity of androgens to stimulate protein synthesis and decrease protein breakdown, especially in muscle, is responsible for the larger muscle mass in men as compared with women. Exogenous androgens (anabolic steroids) are sometimes taken by men and women in an attempt to increase muscle mass.

DEPENDENCE OF SPERMATOGENESIS ON LOWER TEMPERATURES OF THE SCROTUM

Effect on Fertility

For unknown reasons, spermatogenesis ceases at temperatures typical of the abdominal cavity. Thus, when the testes fail to descend before or shortly after birth, and the condition (cryptorchidism) is not surgically corrected, infertility results.

Cooling mechanisms

Normally, the scrotum provides an environment that is 4°C cooler than the abdominal cavity. The cooling is accomplished by a countercurrent heat exchanger located in the spermatic cord. Also, the temperature of the scrotum and the testes is regulated by relative degree of contraction or relaxation of the cremasteric muscles and scrotal skin rugae that surround and suspend the testes.

Effect on FSH and LH

Sertoli cells, and therefore germ cell maturation, are adversely affected by the elevated temperatures of cryptorchid testes. In adults with bilaterally undescended testes, FSH secretion is elevated, probably as a result of decreased Sertoli cell production of inhibins. Testosterone secretion by the Leydig cells of cryptorchid testes also tends to be low, and as a result, LH secretion of adults with bilateral cryptorchidism is elevated.

ERECTION, EMISSION, AND EJACULATION

Erection

Erection is caused by dilation of the blood vessels (a parasympathetic response) in the erectile tissue of the penis (the corpora- and ischiocavernous sinuses). This dilation increases the inflow of blood so much that the penile veins get compressed between the engorged cavernous spaces and the Buck's and dartos fasciae. As a result, for a brief period, inflow of blood to the penis exceeds outflow. Pressure within the penis sometimes equals arterial pressure during a full erection.

Mediators that remove the chronic state of vasoconstriction are probably vasoactive intestinal peptide (VIP) and/or nitric oxide (NO). Acetylcholine may also be involved.

Emission

Emission is the movement of semen from the epididymis, vasa deferentia, seminal vesicles, and prostate to the ejaculatory ducts. The movement is mediated by sympathetic (thoracolumbar) adrenergic transmitters.

Simultaneously with emission, there is also a sympathetic adrenergic-mediated contraction of the internal sphincter of the bladder, which prevents retrograde ejaculation of semen into the bladder. Destruction of this sphincter by prostatectomy often results in retrograde ejaculation.

Emission normally precedes ejaculation but also continues during ejaculation.

Ejaculation

Ejaculation is caused by the rhythmic contraction of the bulbospongiosus and the ischiocavernous muscles, which surround the base of the penis. Contraction of these striated muscles that are innervated by somatic motor nerves causes the semen to exit rapidly in the direction of least resistance, i.e., outwardly through the urethra.

Contrary to commonly held opinion, ejaculation is not parasympathetically mediated; rather, it is mediated by somatic motor efferents.

GONADAL FUNCTION IN THE MALE

The consequences of deficient testosterone production depend upon the age of onset:

- Testosterone deficiency in the second to third month of gestation results in varying degrees of ambiguity in the male genitalia and male pseudohermaphrodism.
- Testosterone deficiency in the third trimester leads to problems in testicular descent (cryptorchidism) along with micropenis.
- Pubertal testosterone deficiency leads to poor secondary sexual development and overall eunuchoid features.
- Postpubertal testosterone deficiency leads to decreased libido, erectile dysfunction, decrease in facial and body hair growth, low energy, and infertility.

Causes of Hypogonadism

- Noonan syndrome
- Klinefelter's syndrome

- Hypothalamic-pituitary disorders (Kallman's syndrome, panhypopituitarism)
- Gonadal failure/sex steroid synthesis failure

Definitions

- Pseudohermaphrodite: an individual with the genetic constitution and gonads of one sex and the genitalia of the other.
- Female pseudohermaphroditism: female fetus exposed to androgens during the 8th to 13th week of development, e.g., congenital virilizing adrenal hyperplasia.
- Male pseudohermaphroditism: lack of androgen activity in male fetus, e.g., defective testes, androgen resistance
- When the loss of receptor function is complete, testicular feminizing syndrome results. Here MIH is present and testosterone is secreted, usually at elevated levels. The external structures are female, but the vagina ends blindly because there are no female internal structures.

Table X-10-1. Hormonal Changes in Specific Altered States

	Sex Steroids	LH	FSH
Primary hypogonadism	↓	↑	↑
Pituitary hypogonadism	↓	↓	↓
Kallman's (↓ GnRH)	↓	↓	↓
Postmenopausal women	↓	↑	↑
Anabolic steroid therapy (male)*	↑	↓	(↓)
Inhibin infusion (male)†	–	–	↓
GnRH infusion (constant rate)‡	↓	↓	↓
GnRH infusion (pulsatile)	↑	↑	↑

*LH suppression causes Leydig cell atrophy in an adult male and therefore reduced testicular androgen production. Because Leydig cell testosterone is required for spermatogenesis, anabolic steroids suppress spermatogenesis.

Although testosterone is not the normal feedback regulating FSH, high circulating testosterone activity will suppress the release of FSH.

†Because FSH is required for spermatogenesis, giving inhibin suppresses spermatogenesis.

‡A constant rate of infusion of the gonadotropin-releasing hormone (GnRH) will cause a transient increase in LH and FSH secretion, followed by a decrease caused by the downregulation of gonadotroph receptors.

Chapter Summary

* GnRH regulates the secretion of both FSH and LH. A pulsatile input of GnRH to the gonadotrophs is required to prevent downregulation of its receptors.
* LH stimulates Leydig cell testosterone, and testosterone is the negative feedback loop for LH. Sertoli cells possess FSH receptors, and inhibin is the normal feedback loop for FSH.
* The testes secrete testosterone and some dihydrotestosterone (DHT). Most of the circulating DHT is due to the peripheral conversion of testosterone.
* Both FSH and Leydig cell testosterone are required for normal spermatogenesis.
* The fetal ovary does not secrete hormones. Regardless of genetics (i.e., XX or XY), without input of the male developmental hormones, the fetus will develop female internal and external structures.
* Normal male development requires testosterone (internal structures), dihydrotestosterone (external structures), and MIH (suppresses female internal structures).
* Erection is mainly a parasympathetic response, whereas ejaculation requires sympathetic involvement.
* Hypogonadism can have many origins, including genetic, structural, environmental, and hormonal.

Female Reproductive System

THE MENSTRUAL CYCLE

The Phases

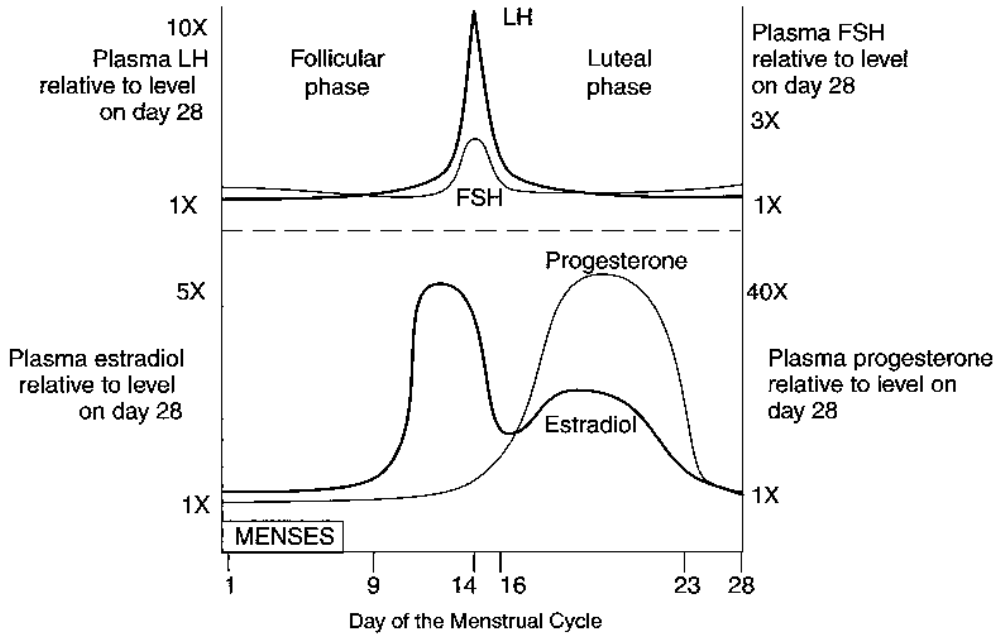
The menstrual cycle (approximately 28 days) can be divided into the following phases or events. By convention, the first day of bleeding (menses) is called day 1 of the menstrual cycle.

- Follicular phase (first 2 weeks) is also called the proliferative or preovulatory phase. This phase is dominated by the peripheral effects of estrogen, which include the replacement of the endometrial cells lost during menses.
- Ovulation (approximately day 14) is preceded by the LH surge, which induces ovulation.
- Luteal phase (approximately 2 weeks) is dominated by the elevated plasma levels of progesterone, and along with the secreted estrogen, creates a secretory quiescent endometrium which prepares the uterus for implantation.
- Menses. Withdrawal of the hormonal support of the endometrium at this time causes necrosis and menstruation.

Follicular phase (approximately days 1 to 14)

- By convention, the first day of bleeding (menses) is called day 1 of the menstrual cycle.
- During the follicular phase, FSH secretion is slightly elevated, causing proliferation of granulosa cells and increased estrogen secretion within a cohort of follicles.
- One follicle, possibly the one with the best blood supply, secretes more estradiol than the others. Because estradiol acts locally within the follicle to increase the granulosa cell's sensitivity to FSH, this follicle becomes the dominant follicle, i.e., the one destined to grow and rupture. The remaining follicles, lacking sufficient FSH, synthesize only androgen and become atretic (die).

Figures X-11-1 through X-11-4 illustrate the hormonal regulation of the menstrual cycle. The graphs represent the plasma hormonal levels throughout the cycle. The length of the menstrual cycle varies, but an average length is 28 days. Each of the plasma hormone concentrations is plotted relative to the day on which its concentration is lowest, i.e., just prior to menses (day 28). The accompanying diagram illustrates specific aspects of the phase under consideration.



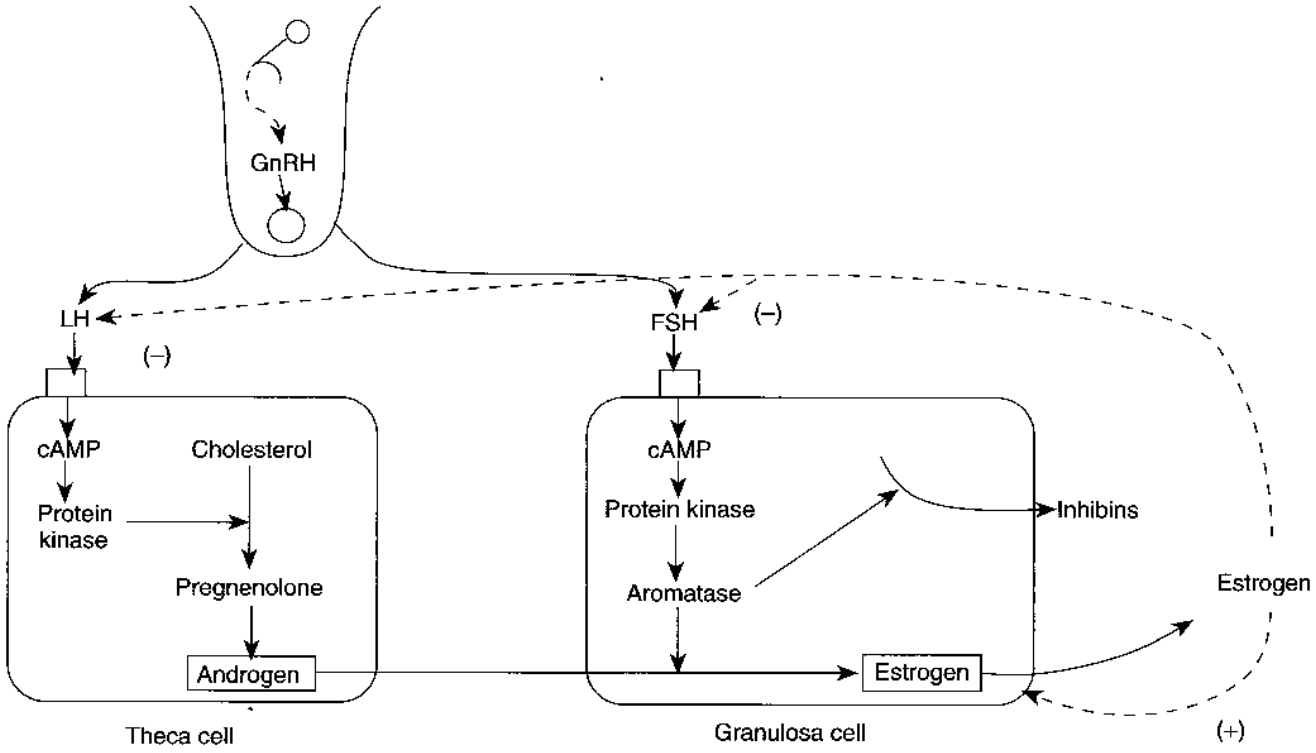


Figure X-11-1. Follicular Phase Relationships Approximately Days 1 to 14

Theca Cells: Under LH stimulation, which acts intracellularly via cAMP, cholesterol is converted to pregnenolone (i.e., desmolase is activated). The pathway continues through intermediates to androgens. Little androgen is secreted; most of the androgen enters the adjacent granulosa cells.

Granulosa Cells: Possess the follicle's only FSH receptors. When coupled to FSH, these act via cAMP to increase the activity of aromatase; aromatase converts the androgens to estrogens (mainly estradiol).

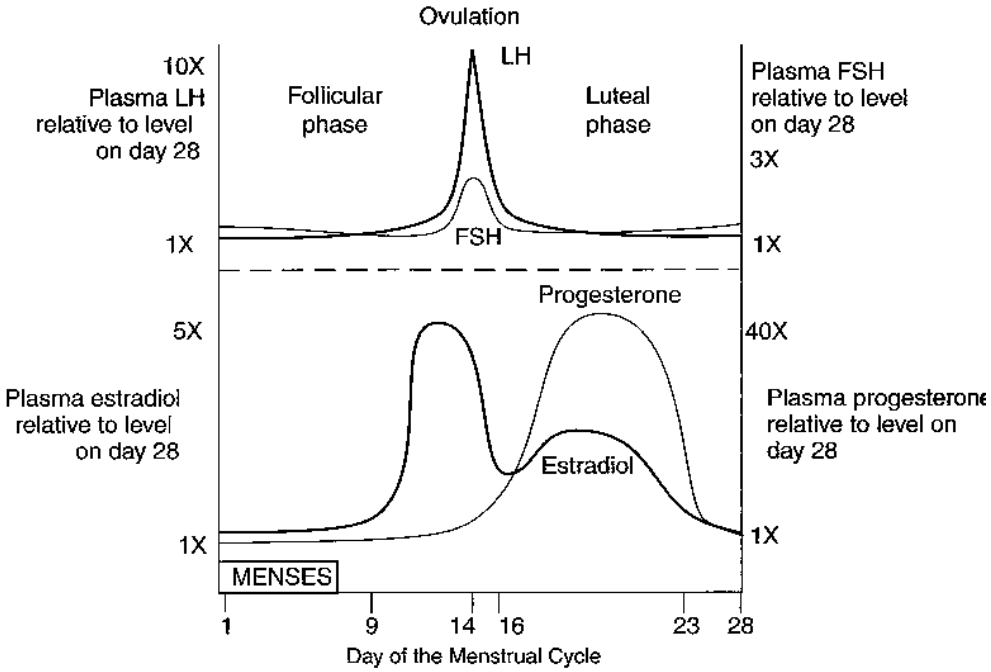
Estrogen: Some of the estrogen produced by the granulosa cells is released into the blood and inhibits the release of LH and FSH from the anterior pituitary. However, another fraction of the estrogen acts locally on granulosa cells, increasing their proliferation and sensitivity to FSH. This local positive effect of estrogens causes a rising level of circulating estrogens during the follicular phase, but at the same time FSH is decreasing because of the inhibitory effect of estrogen on FSH release. Granulosa cells also release inhibins (A and B). Inhibins inhibit the secretion of FSH by the pituitary but their role in the menstral cycle is poorly understood. Activins related to inhibin are also synthesized by the ovary. Activins, opposite to inhibin, will stimulate the release of FSH. However, any physiological effect of activins during the menstral cycle appears to be locally within the ovary.

Peripheral effects of estrogen produced by the granulosa cells during the follicular phase include:

- Circulating estrogens stimulate the female sex accessory organs and secondary sex characteristics.
- Rising levels of estrogens cause the endometrial cells of the uterine mucosal layers to increase their rate of mitotic division (proliferate).
- Circulating estrogens cause the cervical mucus to be thin and watery, making the cervix easy for sperm to traverse.

Ovulation

Ovulation takes place approximately on day 14.



OVULATION OCCURS APPROXIMATELY DAY 14

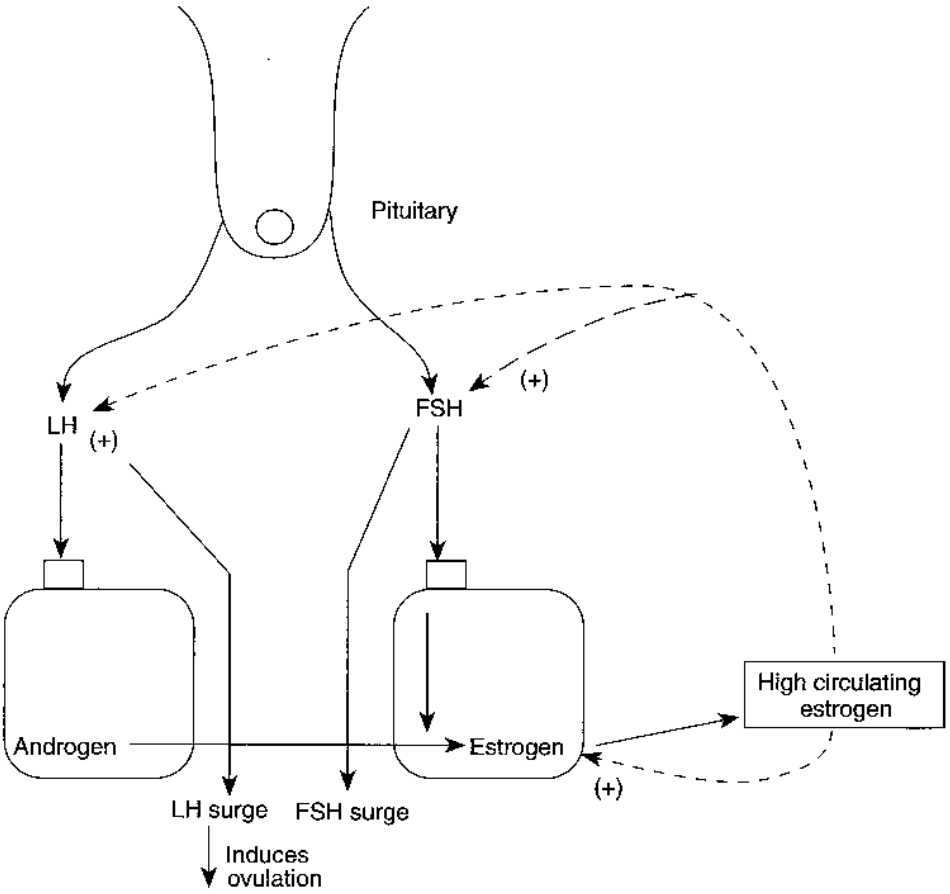


Figure X-11-2. The Pituitary-Ovarian Relationships at Ovulation

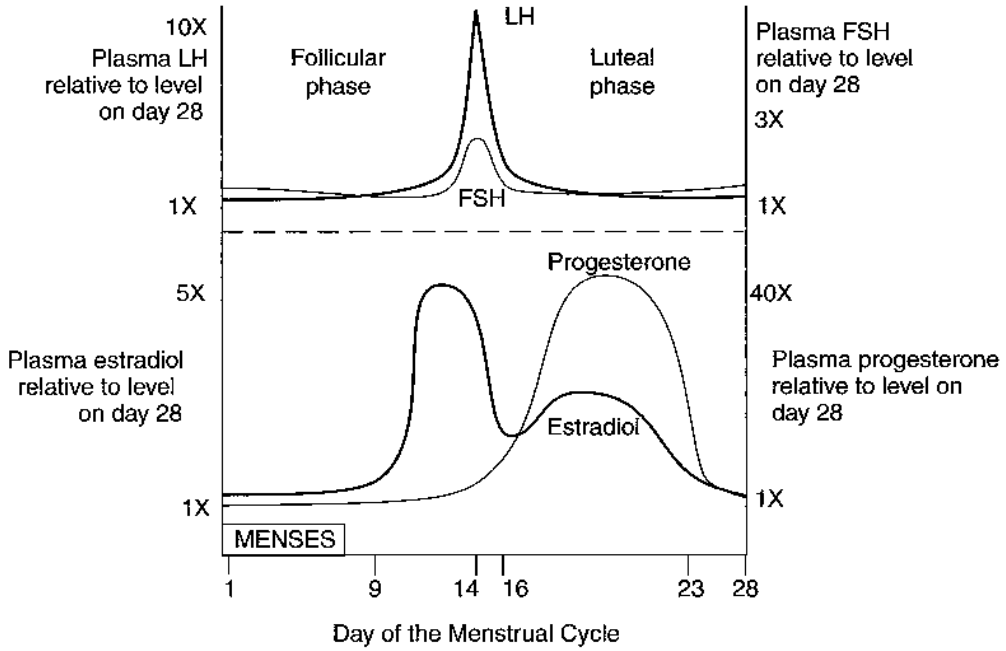
Estrogen Levels

As shown in Figure X-11-2, near the end of the follicular phase, there is a dramatic rise in circulating estrogen. When estrogens rise above a certain level, they no longer inhibit the release of LH and FSH. Instead, they stimulate the release of LH and FSH (negative feedback loop to positive feedback loop).

This causes a surge in the release of LH and FSH. Only the LH surge is essential for the induction of ovulation and formation of the corpus luteum. Notice from the figure that the LH surge and ovulation occur after estrogen peaks. Therefore, if estrogens are still rising, ovulation has not occurred.

Follicular rupture occurs 24–36 hours after the onset of the LH surge. During this time interval, LH removes the restraint upon meiosis, which has been arrested in prophase for years. The first meiotic division is completed, and the first polar body is extruded.

Luteal phase (approximately days 14 to 28)



LUTEINIZATION OF THE PREOVULATORY FOLLICLE

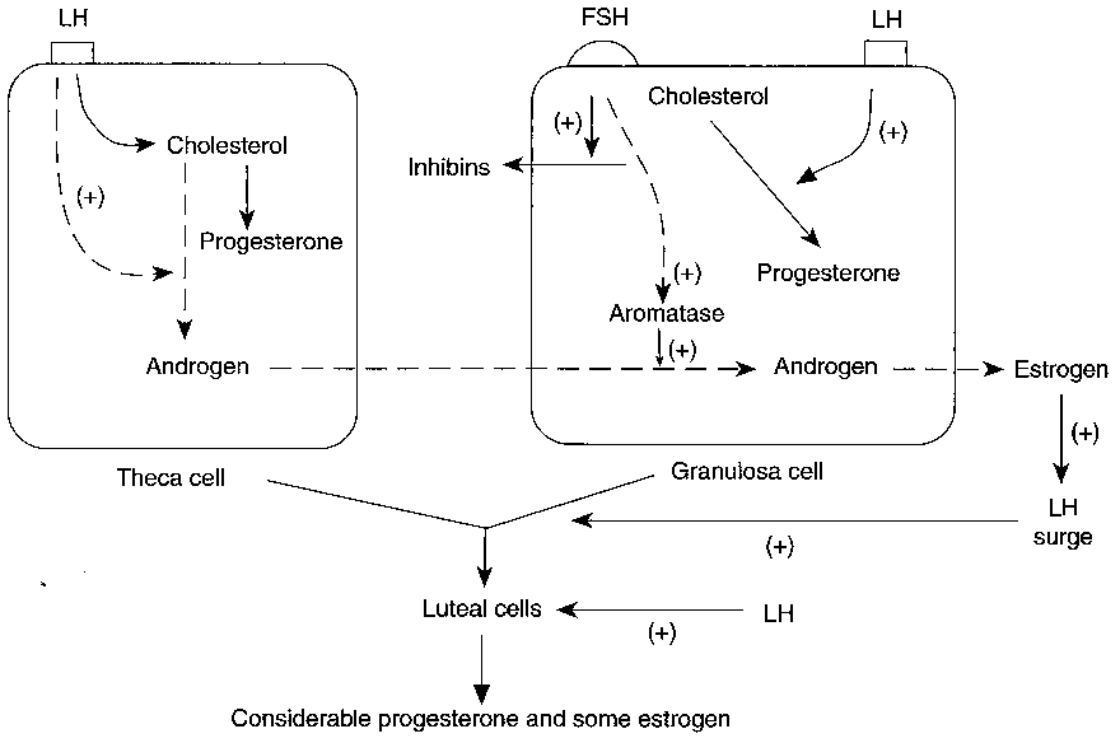


Figure X-11-3. The Luteal Phase Reactions

Preovulatory Follicle

In the latter stages of the follicular phase, intracellular changes within the granulosa and theca cells occur in preparation for their conversion into luteal cells. Estradiol, in conjunction with FSH, causes the granulosa cells to produce LH receptors. The metabolic pathways are then altered to favor the production of progesterone. This would include a decrease in the activity of aromatase and a drop in estrogen production. This is illustrated in Figure X-11-3 (dashed lines represent pathways that are diminishing during the conversion to luteal cells).

LH Surge

Induced by the elevated estrogens, it causes the granulosa cells and theca cells to be transformed into luteal cells and increases the secretion of progesterone.

Corpus Luteum

The process of luteinization occurs following the exit of the oocyte from the follicle. The corpus luteum is made up of the remaining granulose cells, thecal cells, and supportive tissue. Once formed, the luteal cells are stimulated by LH to secrete considerable progesterone and some estrogen. Progesterone inhibits LH secretion (negative feedback).

The increased plasma level of progesterone has several actions:

- It causes the uterine endometrium to become secretory, providing a source of nutrients for the blastocyst.
- It causes the cervical mucus to become thick, sealing off the uterus from further entry of sperm or bacteria.
- It has thermogenic properties, causing the basal body temperature to increase by 0.5–1.0° F.

Menses

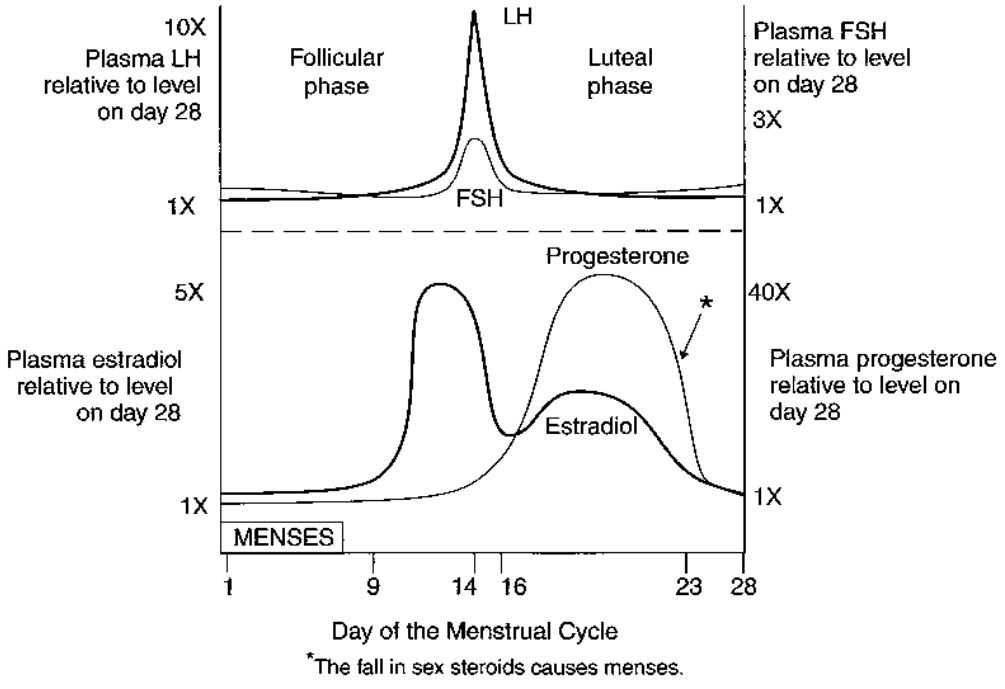


Figure X-11-4. Onset of Menses

Progesterone inhibits the secretion of LH and contributes to the demise of the corpus luteum, because the corpus luteum depends on LH for its continued stimulation. Progesterone secretion decreases not only in response to the decreased LH levels, but also because the luteal cells become less responsive to LH one week after ovulation.

The lower plasma levels of progesterone (and estradiol) no longer support the endometrium, necrosis of the tissue occurs, spiral arterioles break, and menses ensues (loss of the superficial layer of the endometrium, along with some blood).

Menstruation is a passive process due to a lack of gonadal sex steroids.

FEMALE SEX STEROID METABOLISM AND EXCRETION

Solubilization and Excretion

The female sex steroids undergo oxidation or reduction in the liver (and other target tissues), and a glucuronide or sulfate group is attached to the steroidal metabolite. This "conjugation" increases the solubility of the steroids in water, and they thus become excretable in urine.

Estradiol can be excreted as a conjugate of estradiol, but most is first converted to estrone or estriol.

Progesterone is converted in the liver to pregnanediol and is excreted as pregnanediol glucuronide.

Monitoring the Menstrual Cycle

The amount of sex steroids excreted in the urine can be used to monitor the menstrual cycle. For example:

- Low progesterone metabolites and low but slowly rising estrogen metabolites characterize the early follicular phase.
- Low progestone metabolites and rapidly rising estrogen metabolites characterize the latter part of the follicular phase just before ovulation.
- Elevated levels of progesterone metabolites characterize the luteal phase and pregnancy. In the early luteal phase progesterone is rising, in the latter half it is falling.

Estrogens and Androgen Formation

- Estrogen: Generic term for any estrus-producing hormone, natural or synthetic
- 17 β-Estradiol: Major hormone secreted by the ovarian follicle
- Estrone: Some is secreted from the ovary but much is formed in peripheral tissues from androgens. These androgens originate from both the ovary and the adrenal glands. This is the main circulating estrogen following menopause.
- Estriol: Major estrogen synthesized from circulating androgens by the placenta
- Potency: Estradiol > estrone > estriol
- Androgens: The follicles also secrete androgen; DHEA, androstenedione, and testosterone. Additional testosterone production is from the peripheral conversion of adrenal and ovarian androgen. Some testosterone is also converted via 5 α-reductase to dihydrotestosterone in the skin.

New Cycle

During the three days prior to and during menses, plasma levels of progesterone and estradiol are at their low point; negative feedback restraint for gonadotropin secretion is removed. FSH secretion rises slightly and initiates the next cycle of follicular growth.

The length of the follicular phase of the menstrual cycle tends to be more variable than the length of the luteal phase. Long cycles are usually due to a prolonged follicular phase and short cycles to a short follicular phase. Once ovulation has occurred, menses generally follows in about 14 days. The length of the menstrual cycle in days minus 14 gives the most likely day of ovulation.

MENSTRUAL IRREGULARITIES

Amenorrhea

- By definition, amenorrhea means the lack of menstral bleeding.
- Though in itself it does not cause harm, it may be a sign of genetic, endocrine, or anatomic abnormalities.
- In the absence of anatomic abnormalities (and pregnancy), it usually indicates a disruption of the hypothalamic–pituitary axis or an ovarian problem.
- A hypothalamic–pituitary origin would include Kallman's syndrome, functional hypothalamic amenorrhea, amenorrhea in female athletes, eating disorders, hypothyroidism, and pituitary tumors such as prolactinomas.
- Ovarian causes could be premature ovarian failure (premature menopause), repetitive ovulation failure, or anovulation (intermittent bleeding), or a polycystic ovary.

Polycystic Ovarian Syndrome

- Characterized by infertility, hirsutism, obesity, insulin resistance, and amenorrhea or oligomenorrhea
- The enlarged polycystic ovaries are known to be associated with several pathologic findings.
- One theory suggests that it originates as an exaggerated adrenarche in obese girls. The high extraglandular estrogens (mainly estrone) selectively suppress FSH. Ovarian follicles do have a suppressed aromatase activity and thus a diminished capacity to convert androgen into estrogen, but the adrenals may also contribute to the excess androgens as well.
- High androgens promote atresia in developing follicles and disrupt feedback relationships.
- The overall result is annovulation-induced amenorrhea with an estrogen-induced endometrial hyperplasia and breakthrough bleeding.
- Although poorly understood the hyperinsulinemia is believed to be a key etiologic factor.

Hirsutism

- Defined as an excessive generally male pattern of hair growth.
- Virilization refers to accompanying additional alterations, such as deepening of the voice, cliteromegaly, increased muscle bulk, and breast atrophy.
- It is often associated with conditions of androgen excess such as congenital adrenal hyperplasia and polycystic ovarian syndrome.

- Axillary and pubic hair are sensitive to low levels of androgen.
- Hair on the upper chest, face (scalp region not involved), and back require more androgen and represent the pattern seen in males.
- Circulating androgens involved are testosterone, DHEA, DHEAS, and androstenedione in response to LH and ACTH.
- Measurements of DHEAS as well as a dexamethazone suppression test helps in separating an adrenal from an ovarian source.
- Polycystic ovarian syndrome is the most common cause of ovarian androgen excess.

PREGNANCY

Ovum Pickup and Fertilization

In women, the ovum is released from the rupturing follicle into the abdominal cavity, where it is "picked up" by the fimbria of the oviduct. Failure of ovum pickup may result in ectopic pregnancy, i.e., the implantation of the blastocyst at any site other than the interior of the uterus.

Fertilization occurs in the upper end of the oviduct within 8–25 hours after ovulation. After this, the ovum loses its ability to be fertilized. Sperm retain their capacity to fertilize an ovum for as long as 72 hours after ejaculation. For about 48 hours around the time of ovulation the cervical mucus is copious and slightly alkaline. This environment represent a good conduit for the sperm.

Weeks of gestation (gestational age) to estimate the delivery date are commonly taken from the first day of the last menstrual period.

Sperm are transported from the vagina to the upper ends of the oviduct by contraction of the female reproductive tract. The swimming motions of the sperm are important for penetration of the granulosa cell layer (cumulus oophorus) and membranes surrounding the ovum.

Low sperm counts (<20 million/mL of ejaculate) are associated with reduced fertility because sperm from ejaculates with low counts often contain many sperm with poor motility and an abnormal morphology.

Implantation

At the time of implantation, which occurs about 5-7 days after fertilization, the development is at the blastocyst stage. The trophoblastic cells of the fetus now begin to secrete a peptide hormone, human chorionic gonadotropin (hCG).

Fetal hCG possesses a β subunit similar to that of LH, and therefore it has considerable LH activity.

The presence of hCG in the urine can be detected by a variety of test kits for the detection of pregnancy.

Hormonal Maintenance of the Uterine Endometrium

Figure X-11-5 illustrates the production of estrogen and progesterone during pregnancy. The figure is divided into three phases:

- Part of the luteal phase before implantation
- Early pregnancy
- Late pregnancy

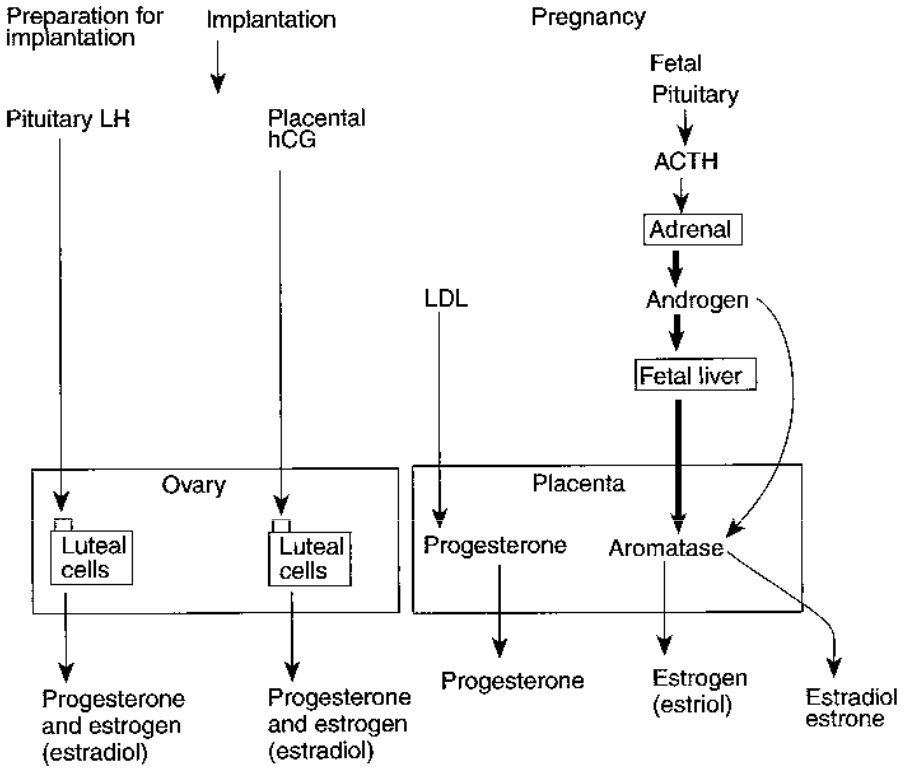


Figure X-11-5. Steroids During Pregnancy

Preparation for implantation (luteal phase)

Pituitary LH stimulates luteal cells to secrete progesterone and some estrogen. Because the ovaries are the source of the estrogen, it is mainly estradiol.

Implantation to second month

At the time of implantation, trophoblastic cells of the fetus begin to secrete hCG. By the 10th day after ovulation, the hCG concentration is sufficiently elevated to stimulate progesterone and estrogen secretion by the corpus luteum, thus rescuing the corpus luteum, which was otherwise destined to regress (i.e., pituitary LH maintains luteal progesterone and estrogen secretion for no more than 10 days after ovulation).

hCG peaks in the first 3 months of pregnancy. During most of that time, hCG is essential for the continued secretion of progesterone and estrogen by the corpus luteum. In the early weeks of pregnancy it doubles in the maternal circulation and is a sensitive marker of early fetal well-being.

Because the corpus luteum does secrete 17-hydroxyprogesterone and the placenta does not, it can be used as a marker of corpus luteum function. Relaxin, also secreted by the corpus luteum, performs a similar function. In both cases the maternal levels drop significantly after the first trimester.

Loss of the corpus luteum during this period would terminate the pregnancy. However, in lieu of the corpus luteum, exogenous progesterone would be a functional substitute.

Third month to term

Placenta secretes enough progesterone and estrogen to maintain the uterus. This is not controlled by hCG. At this time, the ovaries (corpus luteum) can be removed and pregnancy continues.

Progesterone secretion of the placenta is limited only by the amount of precursor (cholesterol) delivered by low-density lipoproteins (LDL) to the placenta. Progesterone maintains uterine quiescence during pregnancy.

Estrogen secretion during pregnancy involves a transfer of steroids from the fetal adrenal cortex and fetal liver to the placenta and then to the maternal circulation.

During midpregnancy, the fetal adrenal cortex, which is as large as the fetal kidney, secretes considerable dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) (weak androgens that do not create problems in a female fetus).

Sequential enzymatic action by the fetal liver and the placenta convert these androgens into estrogens, which enter the maternal circulation. The main estrogen produced is estriol. Rising serum or urinary estriol is considered an excellent index of both placental function and fetal well-being.

Peripheral Effects of Hormonal Changes

The large amount of estrogen and progesterone secreted by the placenta during pregnancy stimulates the following important changes within the mother:

- Massive growth of the uterus, especially the myometrium
- Increased growth of all components (glands, stroma, and fat) of the breasts

Additional hormonal changes

Increased prolactin secretion by the pituitary in response to elevated estrogens

Secretion of human chorionic somatomammotropin (hCS), also referred to as human placental lactogen (hPL), by the placenta (pronounced during the latter half of the pregnancy)

- hCS (hPL) has considerable amino acid sequence homology with growth hormone but has very little growth-stimulating activity.
- hCS (hPL) has metabolic actions similar to growth hormone; that is, it increases maternal lipolysis and ketogenesis and decreases maternal glucose utilization, thereby making maternal energy stores more available for the fetus.
- During the second trimester pregnancy becomes a hyperinsulinemic state with peripheral resistence to the metabolic effects of insulin. This reserves glucose for fetal needs and the mother depends more heavily on fatty acids as a source of energy. Under these conditions even modest fasting can cause ketosis.

- These anti-insulin actions of hCS (hPL) may also account for the gestational diabetes that develops in some pregnant women.
- hCS is secreted in proportion to the size of the placenta and is an index of placental well-being.

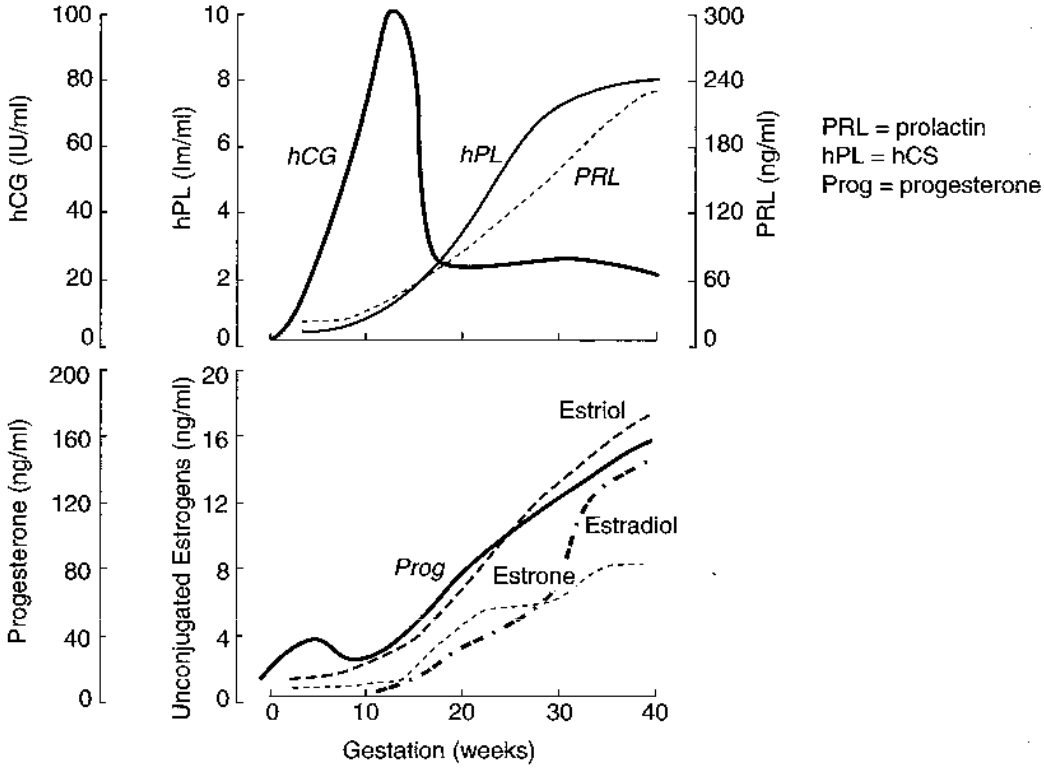


Figure X-11-6. Hormone Levels During Pregnancy

Maternal Compensatory Changes of Pregnancy

Cardiovascular/Renal

Cardiac output increases but TPR decreases and as a result there is no hypertension associated with a normal pregnancy (parallel circuit of placenta). Blood pressure declines in the first trimester and gradually rises toward prepregnancy levels thereafter.

GFR increases and renal threshold decreases. Combined with the increased plasma glucose, glucose often appears in the urine.

Endocrine

The anterior pituitary enlarges by about one-third, due to a hyperplasia of the lactotrophs driven by the rise in estrogen. Postpartum pituitary necrosis (Sheehan syndrome) is preceded by obstetric hemorrhage. The posterior pituitary is usually spared. Failure to lactate is the most common clinical sign. Other manifestations would include the consequences of hypothyroidism and hypocortisolism.

Estrogen increases the circulating steroid-binding globulins and bound hormone increases but FT_4 is normal. Hyperthyroidism increases the risk of preterm delivery. Hypothyroidism is unusual in pregnancy.

Estrogen increases renin secretion, and overall increased activity of the renin-angiotensin-aldosterone system causes fluid retention and hemodilution.

Changes induced near the end of pregnancy

The pubic symphysis, cervix, and vagina become more distensible. These changes make passage of the fetus through the birth canal easier. The peptide hormone relaxin, which is secreted by the ovary, also promotes these changes. Its action is not essential. Parturition in humans is normal in the absence of ovaries.

In response to elevated plasma estrogens, oxytocin receptors increase in the myometrium. Thus, the sensitivity of the uterine myometrium to the excitatory action of oxytocin is increased.

Parturition

The factors that initiate parturition are not well understood, but the following facts are known:

- Although oxytocin can be administered to induce uterine contractions, during normal parturition plasma oxytocin is not elevated until the fetus enters the birth canal (a few minutes before birth).
- Thus, increased oxytocin secretion does not initiate the rhythmic uterine contractions characteristic of the onset of labor.
- Oxytocin does, however, cause the uterus to contract immediately after the fetus is expelled, thus limiting blood flow and blood loss.
- Acting locally on the myometrium, prostaglandins increase contractions. Oxytocin increases uterine synthesis of prostaglandins.
- When a fetus dies, toxic products originating from the fetus increase prostaglandin release in the uterus, thus initiating contractions and a spontaneous abortion (miscarriage). Similarly, administration of prostaglandins induces abortion.

LACTATION

Mammary Gland Growth and Secretion

Growth of mammary tissue is stimulated by the female sex steroids estrogen and progesterone. However, for these steroids to stimulate maximum growth, prolactin, growth hormone, and cortisol also must be present.

During pregnancy, the high levels of plasma estrogen greatly increase prolactin secretion, but milk synthesis does not occur because the high level of estrogen (and progesterone) blocks milk synthesis. At parturition, plasma estrogen drops, withdrawing the block on milk synthesis. As a result, the number of prolactin receptors in mammary tissue increases several-fold, and milk synthesis begins.

Maintaining Lactation

Suckling is required to maintain lactation.

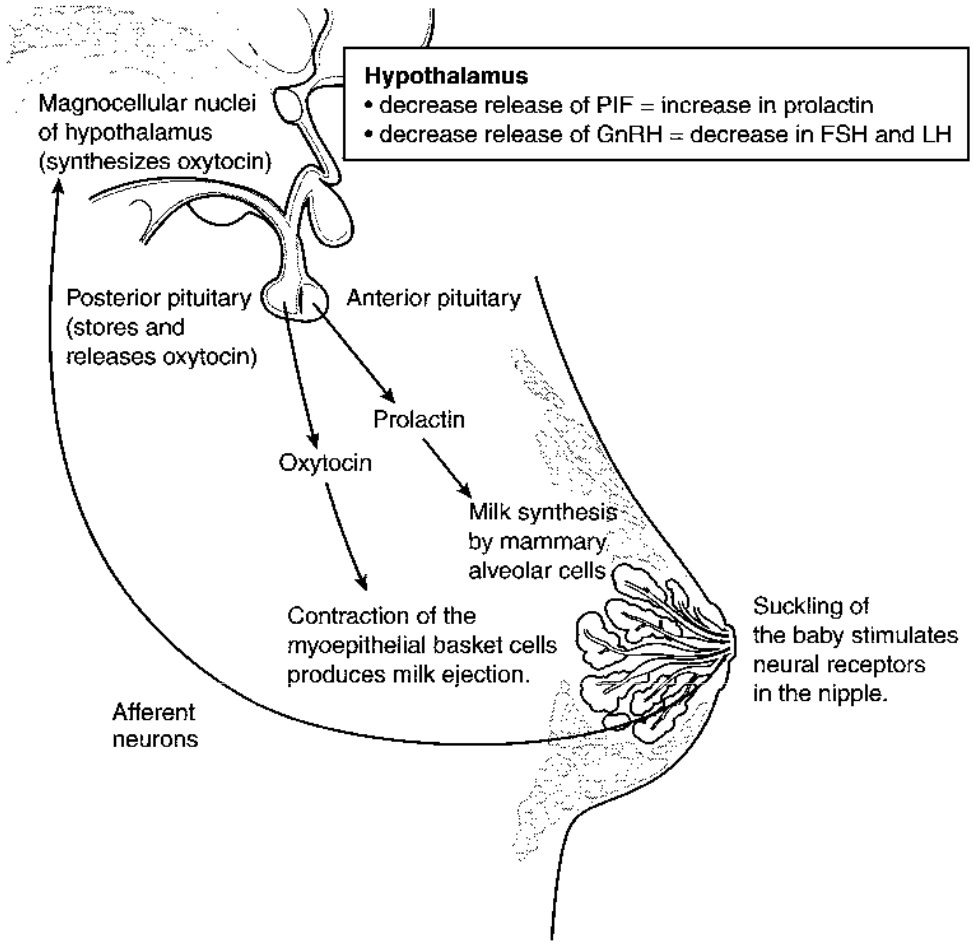


Figure X-11-7. Lactation and the Suckling Reflex

The suckling of the baby at the mother's breast stimulates receptors in the mother's nipples. Signals from these receptors are transmitted to the hypothalamus and have the following effects:

- Oxytocin synthesis and secretion are increased. Oxytocin causes the myoepithelial basket cells that surround the alveoli to contract. Preformed milk is ejected into the ducts and out the openings of the nipple; that is, milk ejection is initiated.
- The release of prolactin-inhibiting factor (PIF = dopamine) by the hypothalamus into the hypophyseal portal vessels is inhibited. This removes a chronic restraint on prolactin secretion. Prolactin secretion increases, and milk secretion is stimulated each time the baby suckles.
- The secretion of GnRH into the hypophyseal portal vessels is inhibited; secretion of FSH and LH decreases. Thus, follicular growth, estrogen secretion, ovulation, and menses cease. High prolactin levels also contribute to the amenorrhea.

For the suckling stimulus to inhibit GnRH secretion completely, the stimulus must be prolonged and frequent. Supplementation of the mother's milk with other fluids or sources of energy reduces the baby's suckling and allows gonadotropin secretion, follicular growth, and ovulation to occur.

Women who do not wish to breastfeed their children are sometimes administered large doses of estrogen. The estrogen inhibits lactation (by its inhibitory action of milk synthesis), even though estrogen promotes increased prolactin secretion.

Chapter Summary

* In the early stages of the follicular phase, estrogen is slowly rising. This is followed by a more rapid rise as ovulation approaches. This latter rise occurs because estrogen acts locally to enhance its own production.
* Once estrogen rises above a certain level, it no longer suppresses LH and FSH secretion but instead enhances their secretion. This induces a surge in the secretion of both LH and FSH. However, only the LH surge is required for ovulation.
* In the luteal phase, LH stimulates the luteal cells to secrete considerable progesterone as well as estrogen. Progesterone in this phase inhibits LH secretion.
* It is the drop in progesterone (and estrogen) that withdraws the hormonal support of the endometrium and that causes menstruation.
* Variations in the length of the menstrual cycle are due to the follicular phase. Once ovulation has occurred, menstruation begins almost exactly 14 days later.
* Fertilization and biological pregnancy occur at the beginning of the luteal phase. Implantation occurs at about the middle of the luteal phase.
* In the first 2 to 3 months of pregnancy, fetal production of hCG is required for continuation of the secretion of progesterone and estrogen by the ovary.
* In pregnancy cardiac output increases, TPR decreases and blood pressure is usually below prepregnancy levels.
* Pregnancy increases GFR and decreases renal threshold.
* Pregnancy is a euthyroid state but there is activation of the renin-angiotensin-aldosterone system, which increases ECF volume.
* The ovaries are not required for the last 6 months of pregnancy because the placenta takes over the secretion of both progesterone and estrogen.
* hCG is an index of fetal well-being in early pregnancy. hPL is an index of placental function later in pregnancy. Estriol in an index of fetal well-being and placental function.
* Postpartum hemorrhaging can cause pituitary infarction (Sheehan's syndrome)
* Near the end of pregnancy, estrogen induces the appearance of oxytocin receptors in the myometrium. Once this occurs, oxytocin can be administered to induce labor. However, it is unlikely that a rise in oxytocin is the natural signal that begins delivery.
* During pregnancy, the rising estrogens are driving an increase in prolactin secretion, but the estrogen also blocks milk synthesis.
* At delivery, it is the drop in estrogen that initiates milk synthesis, but suckling is required to maintain lactation.

SECTION XI

Gastrointestinal Physiology

Gastrointestinal Physiology

GENERAL FEATURES OF THE GASTROINTESTINAL TRACT

Structure

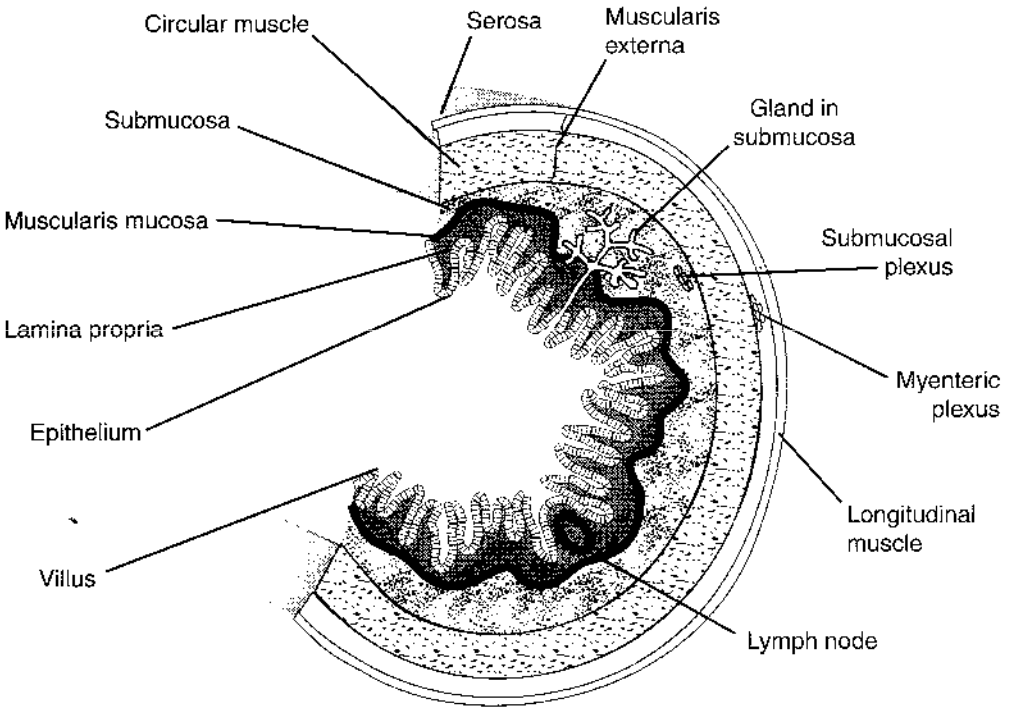


Figure XI-1-1. Gastrointestinal Tract

Mucosa

- Epithelium: consists of a single layer of specialized cells; some are involved in secretions and some release hormones
- Lamina propria: layer of connective tissue which contains glands, hormone-containing cells, lymph nodes, and capillaries
- Muscularis mucosa: a thin layer of muscle, the contraction of which causes folding and ridges in the mucosal layers

Submucosa

- A layer of connective tissue that contains glands, large blood vessels, and lymphatics.
- Outermost region has a nerve net called the submucosal (Meissner's) plexus.
- Meissner's plexus is part of the enteric nervous system and is involved in secretory activity.

Muscularis externa

- Inner layer of circular muscle
- Outer layer of longitudinal muscle
- Myenteric nerve plexus involved in motor activity is between the muscle layers.

Serosa

- Outermost layer of the GI tract
- Consists of connective tissue and a layer of epithelial cells
- Within this layer autonomic nerve fibers run and eventually synapse on target cells and the enteric nerve plexes

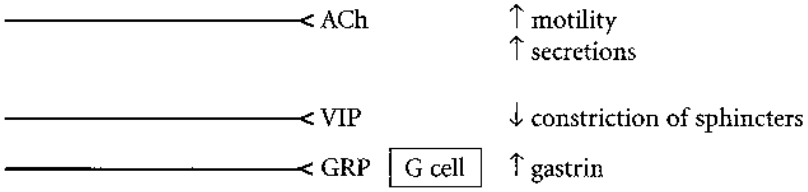
Nervous Control

Sympathetic

The diagram below illustrates how the synaptic junction at the end of a nerve fiber secretes norepinephrine (NE), which then induces responses in the gastrointestinal (GI) system.

An increase in sympathetic activity slows processes.

Parasympathetic



An increase in parasympathetic activity promotes digestive and absorptive processes.

VIP = vasoactive intestinal peptide, an inhibitory parasympathetic transmitter

GRP = gastrin-releasing peptide; stimulates the release of gastrin from G cells

Endocrine Control

Table XI-1-1. The Endocrine Control of the GI System

Hormone**	Source	Stimulus	Stomach Motility and Secretion	Pancreas	Gallbladder
Secretin	S cells lining duodenum	Acid entering duodenum	Inhibits	Stimulates fluid secretion (HCO_3^-)	
CCK	Cells lining duodenum	Fat and amino acids entering duodenum	Inhibits emptying	Stimulates enzyme secretion	1. Contraction 2. Relaxation sphincter (Oddi)
Gastrin	G cells of stomach Antrum Duodenum	Stomach distension Parasym (GRP) Peptides Stomach acid inhibits*	Stimulates		
GIP	Duodenum	Fat, CHO, amino acids	Inhibits		

CCK = cholecystokinin; GIP = gastric inhibitory peptide (glucose insulinotropic peptide)

*Note: In a non–acid-producing stomach (e.g., chronic gastritis), the reduced negative feedback increases circulating gastrin.

**All four hormones stimulate insulin release.

MOTILITY

Characteristics of Smooth Muscle

Electrical activity

- Resting membrane potential -40 to -65 mV
- Oscillation of membrane potential is generated by interstitial cells that act as pacemakers. This is referred to as slow waves or basic electrical rhythm, and if threshold is reached it generates action potentials.
- Action potentials are generated by the opening of slow channels that allow the entry of both sodium and calcium.

Motor activity

- Stretch produces a contractile response.
- Gap junctions create an electrical syncytium within the smooth muscle.
- Slow waves create low level contractions, and action potentials strengthen the contractions.
- Pacemaker activity from the interstitial cells creates the intrinsic motor activity.
- Tonic contraction at sphincters act as valves.

Swallowing

Swallowing is a reflex controlled from the brain stem.

Efferent input is via the vagus nerve for all events, and these are summarized in Figure XI-1-2.

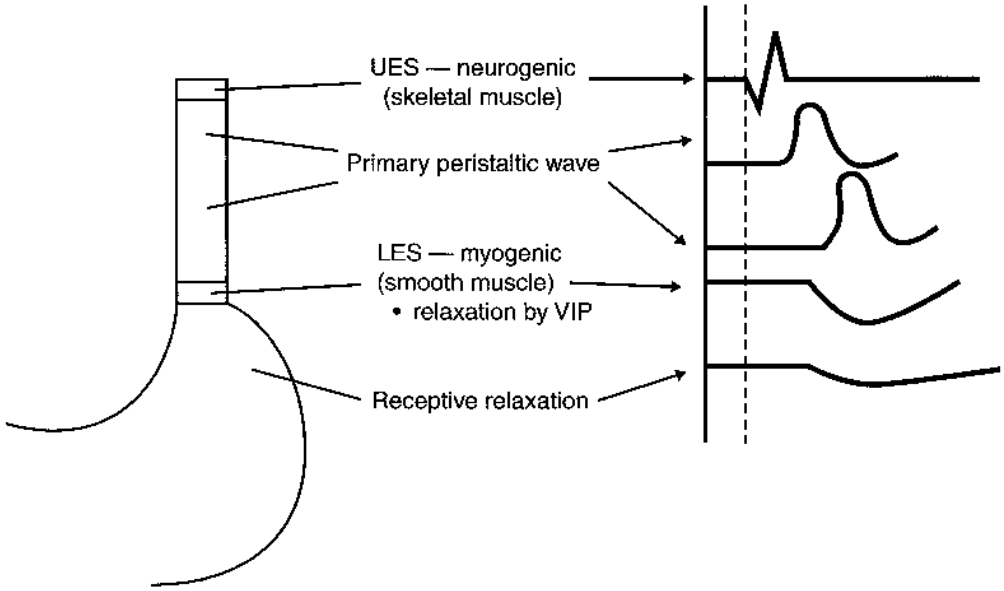


Figure XI-1-2. Swallowing, the Peristaltic Wave

An increase in sympathetic activity slows processes.

Events during swallowing:

- Relaxation of upper esophageal skeletal muscle sphincter (UES)
- Primary peristaltic wave
- Relaxation of lower esophageal smooth muscle sphincter (LES) via VIP acting as an inhibitory transmitter
- Relaxation of proximal stomach (receptive relaxation)

If the primary peristaltic wave is not successful, a secondary peristaltic wave will be initiated by a local distension of the esophagus.

In achalasia, the LES fails to relax during a swallow, due to abnormalities of the enteric nerves. Primary peristalsis in the esophageal body is poor. Swallowed food is retained in the esophagus. The pressure wave in the esophagus is weak; resting pressure in the LES is abnormally high and does not decrease to allow passage of the swallowed material.

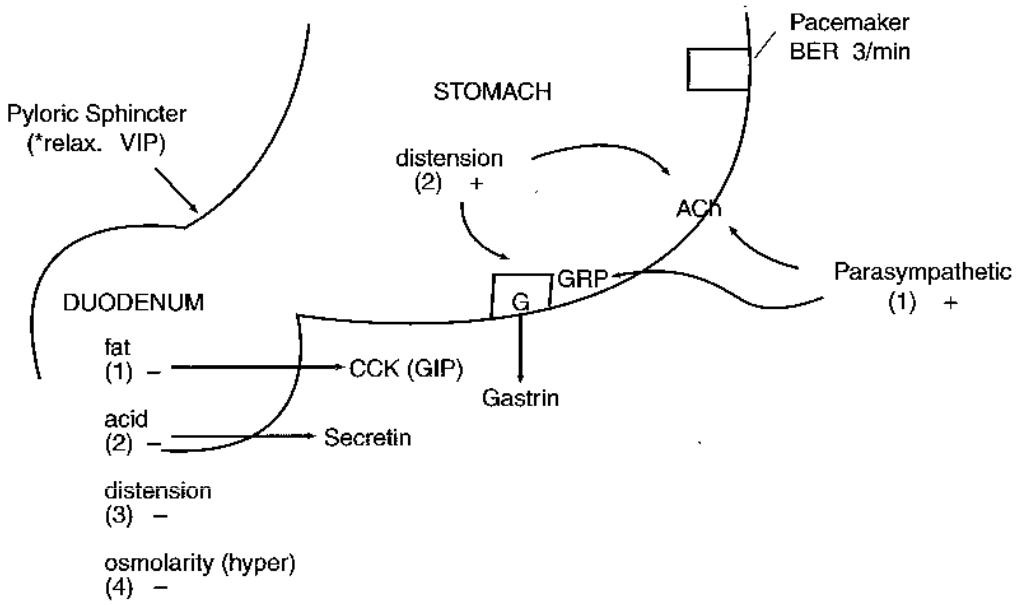
In reflux esophagitis, the LES does not maintain adequate tone. The reflux of stomach acid into the esophagus presents serious risk of erosion. Scleroderma may present with reflux due to inadequate LES tone and difficulty swallowing due to poor development of propulsive pressure.

Diffuse esophageal spasm is another neuromuscular disorder of the esophagus. It may present with severe chest pain resembling a heart attack. Barium swallowing reveals repeated, spontaneous waves of contraction.

These disorders typically cause problems with the swallowing of both solids and liquids. Difficulty of swallowing solids only usually indicates a mechanical obstruction. Difficulty initiating swallowing, oropharyngeal dysphagia, is usually neural in origin.

Gastric Motility

The primary factors and additional aspects are illustrated in Figure XI-1-3.



Abbreviations

ACh = Acetylcholine
BER = Basic electrical rhythm
GIP = Gastric inhibitory polypeptide
GRP = Gastrin-releasing peptide
VIP = Vasoactive intestinal polypeptide
+ stimulates motility
– inhibits motility

Figure XI-1-3. Endocrine and Neural Control of the Stomach

Stimulation

Increased parasympathetic activity via acetylcholine and gastrin release

Local distension

Inhibition

Low pH of stomach contents inhibits the release of gastrin

Feedback from duodenal overload (neural and hormonal)

Stomach Emptying

Liquids > CHO > protein > fat (> = faster than)

The pyloris of the stomach acts as a sphincter to control the rate of stomach emptying. A wave of contraction closes the sphincter so that only a small volume is moved forward into the duodenum. CCK, GIP, and secretin will increase the degree of pyloric constriction and will slow stomach emptying.

Small Intestinal Motility

- Rhythmic contractions in adjacent sections create segmentation contractions, which are mixing movements.
- Waves of contractions preceded by a relaxation of the muscle (peristaltic movements) are propulsive.
- The ileocecal sphincter, or valve between the small and large intestine, is normally closed.
- Distension of the ileum creates a muscular wave that relaxes the sphincter.
- Distension of the colon creates a nervous reflex to constrict the sphincter.

Colon Motility

- Segmentation contractions create bulges (haustrations) along the colon.
- Mass movements, which are propulsive, are more prolonged than the peristaltic movements of the small intestine.

Migrating Myoelectric Complex (MMC)

- A propulsive movement initiated during fasting, which begins in the stomach and moves undigested material from the stomach and small intestine into the colon.
- Repeats every 90–120 minutes during fasting.
- When one movement reaches the distal ileum, a new one starts in the stomach.
- Correlated with high circulating levels of motilin, a hormone of the small intestine
- This movement prevents the backflow of bacteria from the colon into the ileum and its subsequent overgrowth in the distal ileum.

Defecation

- Defecation is a reflex involving the central nervous system.
- A mass movement in the terminal colon fills the rectum and causes a reflex relaxation of the internal anal sphincter and a reflex contraction of the external anal sphincter.
- Voluntary relaxation of the external sphincter accompanied with propulsive contraction of the distal colon complete defecation.
- Lack of a functional innervation of the external sphincter causes involuntary defecation when the rectum fills.

SECRETIONS

Salivary Secretions

- Parotid gland secretions are entirely serous (lack mucin).
- Submandibular and sublingual gland secretions are mixed mucus and serous.
- They are almost entirely under the control of the parasympathetic system, which promotes secretion.
- The initial fluid formation in the acinus is via an indirect chloride pump (secondary active transport powered by the Na/K ATPase pump), and the electrolyte composition is isotonic and similar to interstitial fluid.
- NaCl is reabsorbed in the ducts, and because the water cannot follow the final secretions are hypotonic.

Many of these features are illustrated in Figure XI-1-4.

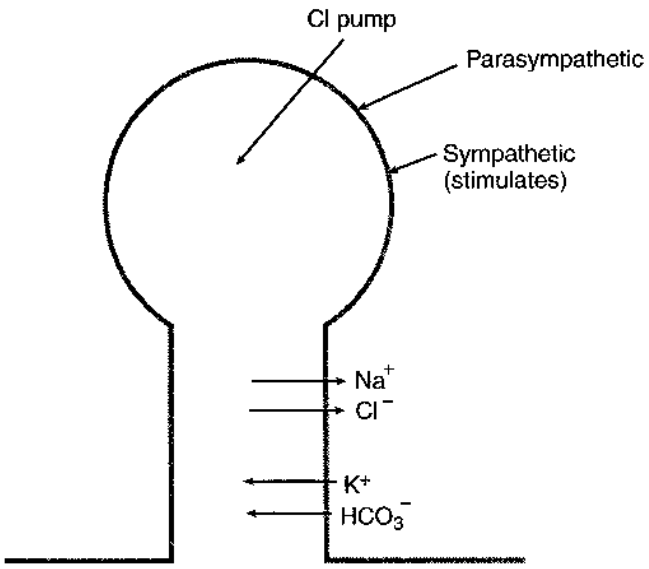


Figure XI-1-4. Salivary Secretion

Composition of salivary secretions

- Low in Na^+, Cl^- because of reabsorption
- High in K^+, HCO3 because of secretion (pH = 8)
- α-Amylase (ptyalin): secreted in the active form and begins the digestion of carbohydrates
- Mucus, glycoprotein
- Immunoglobulins and lysozymes
- Low tonicity: Salivary fluid is hypotonic because of reabsorption of NaCl and impermeability of ducts to water.

Gastric Secretions

- The epithelial cells that cover the gastric mucosa secrete a highly viscous alkaline fluid (mucin plus bicarbonate) that protects the stomach lining from the caustic action of HCl.
- Fluid needs both mucin and bicarbonate to be protective.
- Nonsteroidal anti-inflammatory drugs such as aspirin decrease the secretion of the mucin and bicarbonate.
- Surface of the mucosa studded with the openings of the gastric glands
- Except for the upper cardiac region and lower pyloric region whose glands secrete mainly a mucoid fluid, gastric glands secrete a fluid whose pH can be initially as low as 1.0.

Secretions of the main cells composing the oxyntic gastric glands

Parietal cells

- HCl
- Intrinsic factor combines with vitamin B_{12} and is reabsorbed in the distal ileum. This is the only substance secreted by the stomach that is required for survival. It is released by the same stimuli that release HCl.

Chief Cells

Pepsinogen is converted to pepsin by H^+, as illustrated in the diagram below.

$$\text{Pepsinogen} \xrightarrow{H^+} \text{pepsin (proteins to peptides)}$$

- Pepsinogen is initially converted to active pepsin by acid.
- Active pepsin continues the process.
- Pepsin is active only in the acid pH medium of the stomach.
- Pepsin begins the digestion of protein.

Mucous Neck Cells

- Secrete the protective mucus, HCO_3 combination

Ionic composition of gastric secretions

- Compared with extracellular fluid, gastric secretions are high in H^+, K^+, Cl^-, but low in Na^+. The greater the secretion rate, the higher the H^+ and the lower the Na^+.
- Vomiting stomach contents produces a metabolic alkalosis and a loss of body potassium (hypokalemia mainly due to the alkalosis effect on the kidney).

Control of acid secretion

There are three natural substances that stimulate parietal cells:

- Acetylcholine, acting as a transmitter
- Locally released histamine
- The hormone gastrin

Distension of the stomach following a meal stimulates mechanoreceptors from which the reflex afferents and efferents run in the vagus (vagovagal reflex). The factors that stimulate the parietal cells also stimulate the chief cells. Once the pH of stomach contents decreases to 2.0, negative feedback factors strongly inhibit further acid secretion.

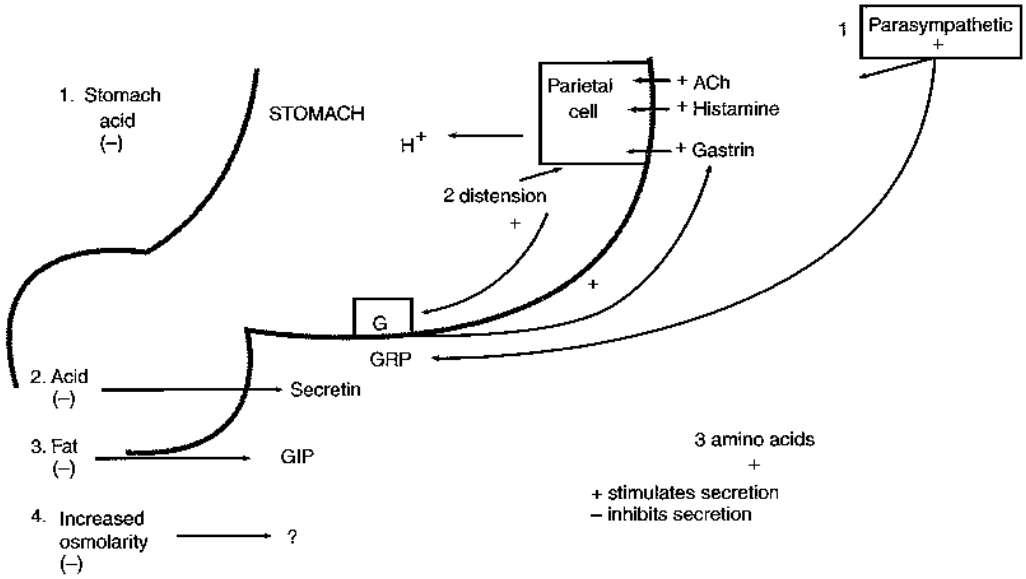


Figure XI-1-5. Control of Gastric Acid Secretion

Cellular mechanisms of acid secretion

- Within the cell, carbonic anhydrase facilitates the conversion of CO_2 into H^+ and HCO_3^-.
- The demand for CO_2 can be so great following a meal that the parietial cells extract CO_2 from the arterial blood.
- Hydrogen ions are secreted by a H/K-ATPase pump similar to that in the distal nephron.
- The pumping of H^+ raises intracellular HCO_3^- and its gradient across the basal membrane and provides the net force for pumping Cl^- into the cell.
- The chloride diffuses through channels across the apical membrane, creating a negative potential in the stomach lumen.
- Because of the extraction of CO_2 and secretion of HCO_3^-, the venous blood leaving the stomach following a meal is alkaline.

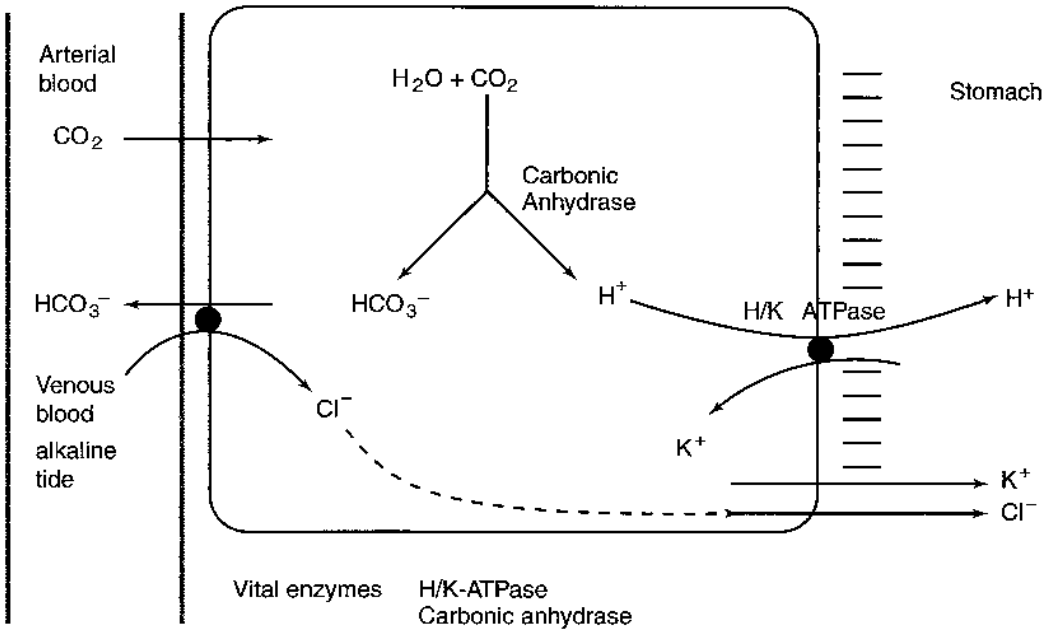


Figure XI-1-6. Regulation of Parietal Cell Secretion

Pancreatic Secretions

- Exocrine tissue is organized into acini and ducts very similar to that of the salivary glands.
- Cholinergic nerves to the pancreas stimulate the secretion of both the enzyme and aqueous component.
- Food in the stomach stimulates stretch receptors and, via vagovagal reflexes, stimulates a small secretory volume.
- Sympathetics inhibit secretion.
- Most of the control is via secretin and CCK.

Enzymatic components

- Trypsin inhibitor, a protein present in pancreatic secretions, prevents activation of the proteases within the pancreas.
- In addition to the following groups of enzymes, pancreatic fluid contains ribonucleases and deoxyribonucleases.
- A diet high in one type of food (protein, CHO, fat) will result in the preferential production of enzymes for that particular food.

Pancreatic amylases are secreted as active enzymes:

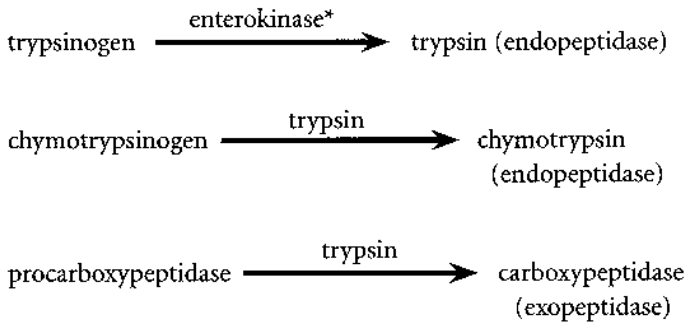
- Hydrolyze α-1,4-glucoside linkage of complex carbohydrates, forming three smaller compounds:
  - α-Limit dextrins: still a branched polysaccharide
  - Maltotriose, a trisaccharide
  - Maltose, a disaccharide
- Cannot hydrolyze β linkages of cellulose

Pancreatic lipases are mainly secreted as active enzymes. Glycerol ester lipase (pancreatic lipase) needs colipase to be effective. Colipase displaces bile salt from the surface of micelles. This allows pancreatic lipase to attach to the droplet and digest it, leading to formation of two free fatty acids and one monoglyceride (a 2-monoglyceride, i.e., an ester on carbon 2).

Cholesterol esterase (sterol lipase) hydrolyzes cholesterol esters to yield cholesterol and fatty acids. **Pancreatic proteases** are secreted as inactive zymogens. They include trypsinogen, chymotrypsinogen, and procarboxypeptidase.

Activation Sequence

The activation sequences are summarized below.



*Enterokinase (also known as enteropeptidase) is an enzyme secreted by the lining of the small intestine. It is not a brush border enzyme. It functions to activate some trypsinogen, and the active trypsin generated activates the remaining proteases.

Fluid and electrolyte components

- Aqueous component is secreted by epithelial cells which line the ducts.
- Fluid is isotonic due to the high permeability of the ducts to water and the concentrations of Na and K are the same as plasma.
- Bicarbonate and chloride concentrations vary reciprocally. High flow, high bicarbonate, low chloride
- The high bicarbonate in the lumen is created by a secondary active transport
- Entry of chloride across the apical membrane into the lumen is via a chloride channel.
- In cystic fibrosis there is a mutation in the gene that encodes this channel, resulting in less chloride and a reduced fluid component of pancreatic secretions. The smaller volume of highly viscous fluid may also contain few enzymes.

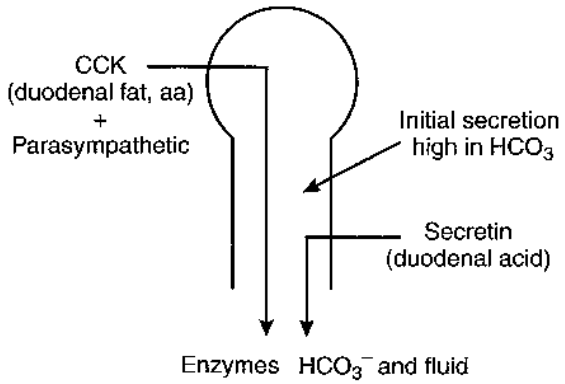


Figure XI-1-7. Control of the Exocrine Pancreas

Control of pancreatic secretions

Most of the regulation is via two hormones: secretin and cholecystokinin

Secretin

- Released from the duodenum in response to acid entering from the stomach.
- Action on the pancreas is the release of fluid high in HCO_3^-.
- This released HCO_3^--rich fluid is the main mechanism that neutralizes stomach acid entering the duodenum.

Cholecystokinin (CCK)

- Released from the duodenum in response to partially digested materials (e.g., fat, petides, and amino acids)
- Action on the pancreas is the release of enzymes (amylases, lipases, proteases).

Composition and Formation of Bile

Overview

Figure XI-1-8 summarizes the major components of bile. A complete description follows.

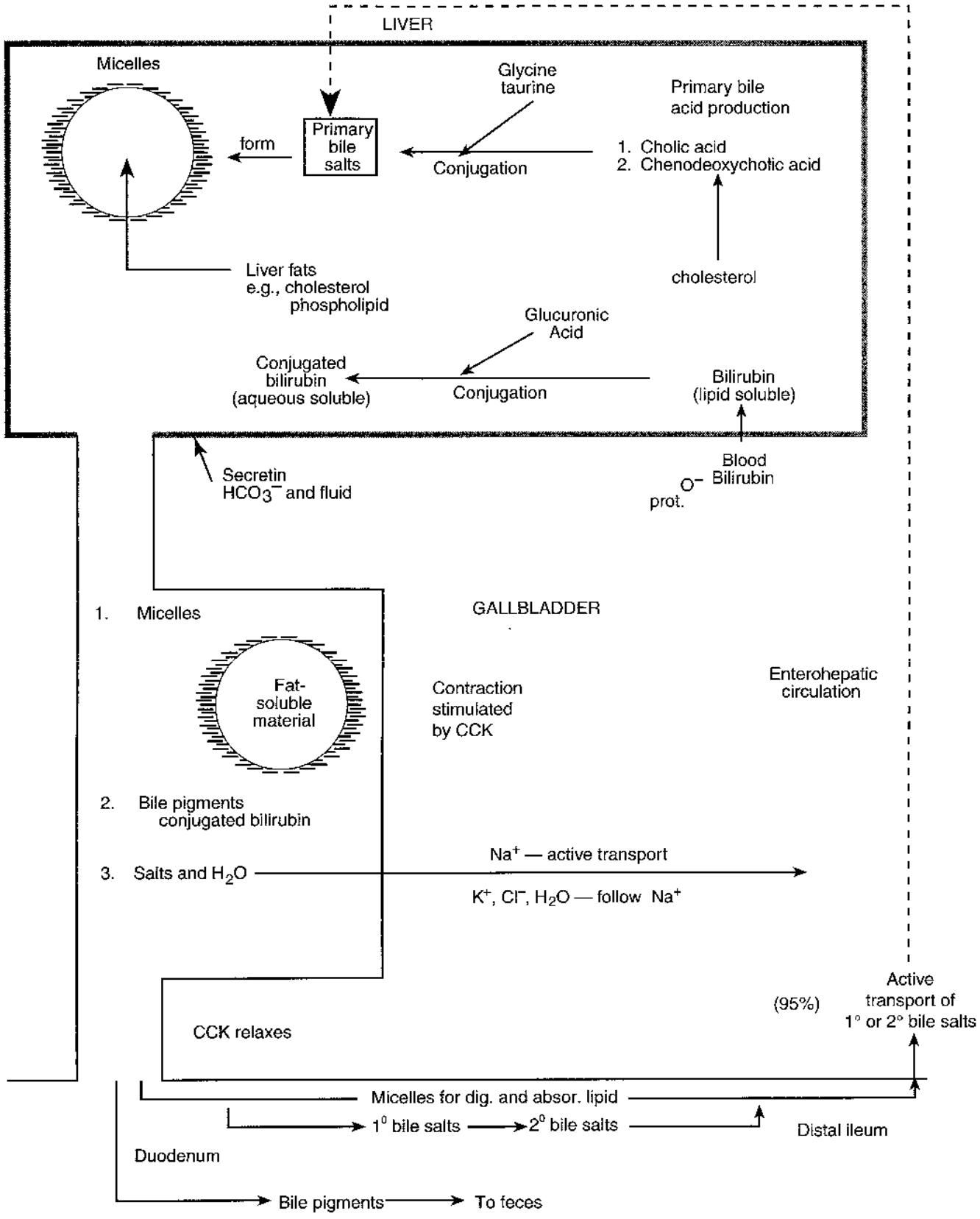


Figure XI-1-8. Production and Metabolism of Bile

Bile salts and micelles

Primary bile acids known as cholic acid and chenodeoxycholic acid are synthesized by the liver from cholesterol. The lipid-soluble bile acids are then conjugated primarily with glycine. The conjugated forms are water-soluble but contain a lipid-soluble segment. Because they are ionized at neutral pH, conjugated bile acids exist as salts of cations (Na^+) and are, therefore, called bile salts.

Bile salts are actively secreted by the liver.

Secondary bile acids are formed by deconjugation and dehydroxylation of the primary bile salts by intestinal bacteria, forming deoxycholic acid (from cholic acid) and lithocholic acid (from chenodeoxycholic acid). Lithocholic acid has hepatotoxic activity and is excreted.

Micelle Formation

When bile salts become concentrated, they form micelles. These are water-soluble spheres with a lipid-soluble interior. As such, they provide a vehicle to transport lipid-soluble materials in the aqueous medium of the bile fluid and the small intestine.

Micelle Function

Micelles are vital in the digestion, transport, and absorption of lipid-soluble substances from the duodenum to the distal ileum. In the distal ileum, and only in the distal ileum, can the bile salts be actively reabsorbed and recycled (enterohepatic circulation). Lack of active reabsorbing mechanisms (or a distal ileal resection) causes loss in the stool and a general deficiency in bile salts, as the liver has a limited capacity to manufacture them. This deficiency can lead to fat malabsorption and cholesterol gallstones.

Bile pigments

Bilirubin

A major bile pigment, bilirubin is a lipid-soluble metabolite of hemoglobin. Transported to the liver attached to protein, it is then conjugated and excreted as water-soluble glucuronides. These give a golden yellow color to bile.

Stercobilin

Produced from metabolism of bilirubin by intestinal bacteria. It gives a brown color to the stool.

Salts and water

The HCO_3^- component is increased by the action of secretin on the liver.

The active pumping of sodium in the gallbladder causes electrolyte and water reabsorption, which concentrates the bile.

Bile pigments and bile salts are not reabsorbed from the gallbladder.

Phospholipids (mainly lecithin)

Insoluble in water but are solubilized by bile salt micelles

Cholesterol

Present in small amounts. It is insoluble in water and must be solubilized by bile salt micelles before it can be secreted in the bile.

Control of bile secretion and gallbladder contraction

- Secretin causes secretion of HCO_3^- and fluid into bile canalicular ducts.
- Secretion of bile salts by hepatocytes is directly proportional to hepatic portal vein concentration of bile salts.
- CCK causes gallbladder contraction and sphincter of Oddi relaxation.

Small Intestinal Secretions

- Most prominent feature of the small intestine is the villi.
- Surface epithelial cells display microvilli.
- Water and electrolyte reabsorption greatest at the villus tip.
- Water and electrolyte secretion greatest at the bottom in the crypts of Lieberkuhn.

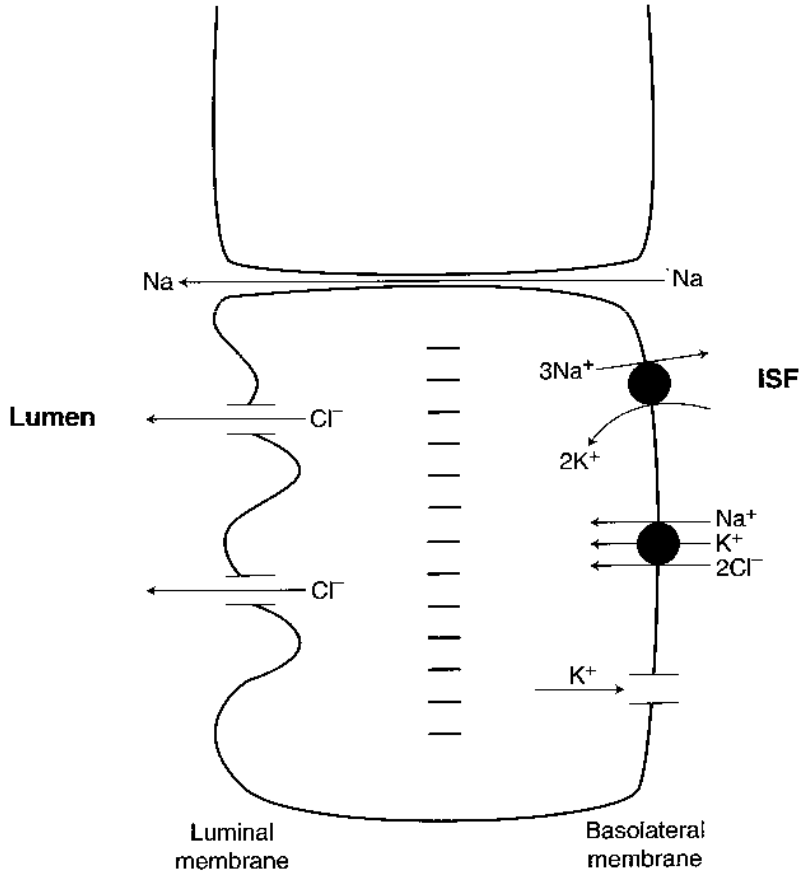


Figure XI-1-9. Secretion of Electrolytes by a Crypt Cell of the Small Intestine

Crypt secretion

- A Na-K-Cl transporter in the basolateral membrane facilitates the ion uptake by secondary active transport.
- Na entry drives the entry of K and Cl against their electrochemical gradients.
- The elevated intracellular Cl and negative intracellular potential drives the diffusion of chloride through channels on the apical membrane.
- Luminal Cl then pulls water, Na, and other ions into the lumen, creating the isotonic secretion. This is the general scheme of the chloride pump.
- Neurotransmitter secretagogues include VIP and ACh.
- Luminal secretagogues include bacterial toxins.
- A cholera toxin strongly activates the apical Cl channels of the crypts, increasing water and electrolyte secretion.
- A glucose-containing solution counters (see absorption section) by driving an increased water and electrolyte reabsorption.

DIGESTION

General Features

- Figure XI-1-10 summarizes the regional entry of the major digestive enzymes proceeding from the mouth, stomach, and through the small intestine. A text summary follows.

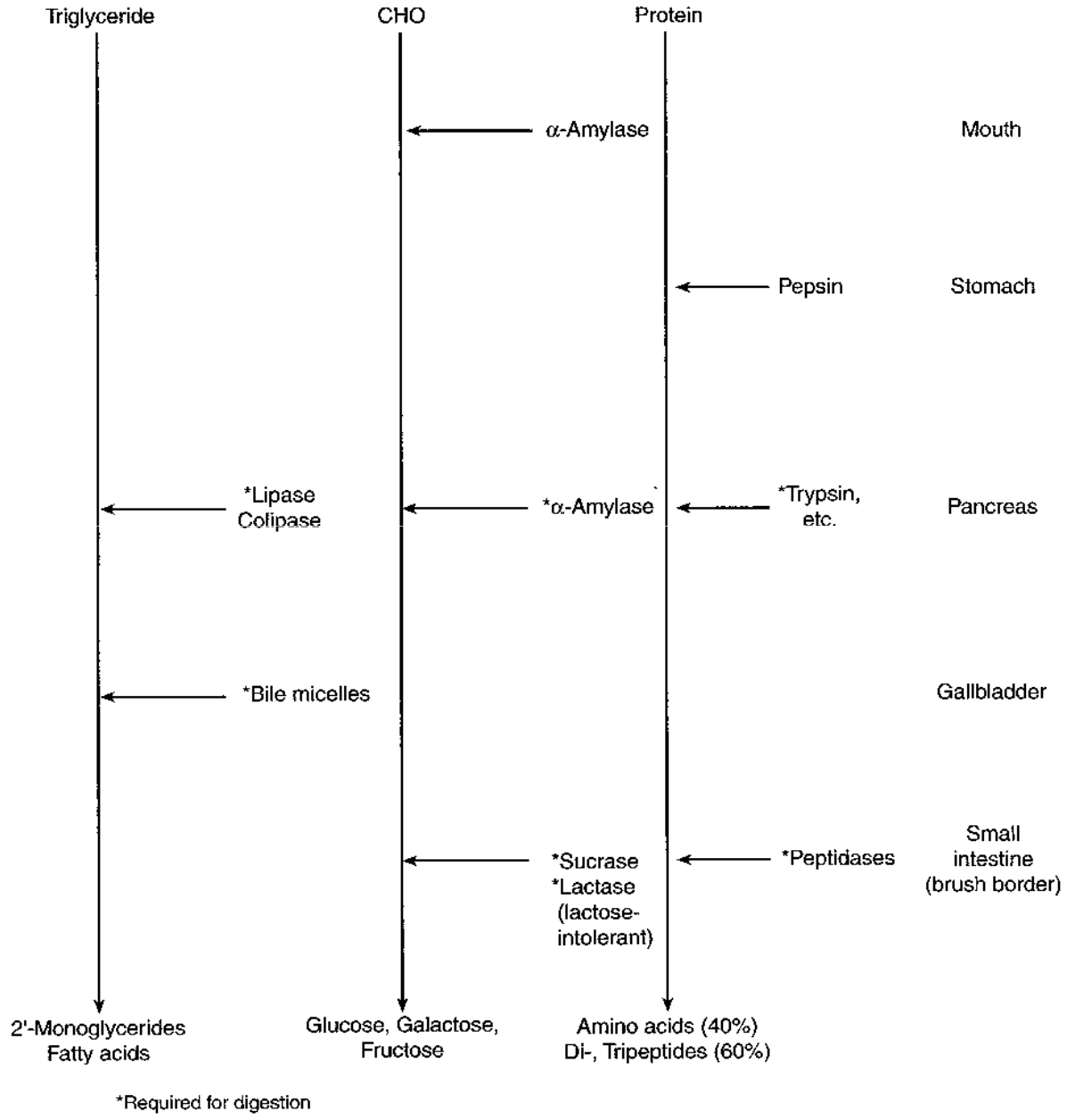


Figure XI-1-10. Summary of Digestive Processes

Summary of Digestive Enzymes and End Products

Triglycerides

Stomach: Fatty materials are pulverized to decrease particle size and increase surface area.

Small intestine: Bile micelles emulsify the fat, and pancreatic lipases digest it. Micelles and pancreatic lipase are required for triglyceride digestion. The major end products are 2-monoglycerides and fatty acids.

Carbohydrates

Mouth: Salivary α-amylase begins the digestion, and its activity continues in the stomach until acid penetrates the bolus; however, it is not a required enzyme.

Small intestine: Pancreatic α-amylase, a required enzyme for CHO digestion, continues the process. Hydrolysis of starch by α-amylase goes on in solution in the lumen of the small intestine, mostly in the duodenum. Further processing or splitting of these trisaccharides, disaccharides, and oligosaccharides is necessary but does not take place in solution; rather, it occurs on the brush border. The enzymes—α-dextrinase (or α-glucoamylase), isomaltase, and maltase—are all bound to the brush border (apical membrane of enterocytes). Brush border enzymes have their highest activity in the jejunum (upper). These brush border enzymes are required for digestion mainly because disaccharides—e.g., sucrose, lactose—are not absorbed from the gut.

- The α-dextrinase cleaves terminal α-1,4 bonds, producing free glucose.
- Lactase hydrolyzes lactose into glucose and galactose. Lactase deficiency (lactose intolerance) leads to osmotic diarrhea.
- Sucrase splits sucrose into glucose and fructose.
- Maltase (also a brush border enzyme) breaks down the maltose and maltotriose to form 2 and 3 glucose units, respectively.
- The monosaccharide end products—glucose, galactose, and fructose—are readily absorbed from the small intestine, also mainly in the jejunum.

Proteins

Stomach: Pepsin begins the digestion of protein in the acid medium of the stomach; however, it is not an essential enzyme.

Small intestine: Digestion continues with the pancreatic proteases (trypsin, chymotrypsin, elastase, and carboxypeptidases A and B), which are essential enzymes.

All these pancreatic enzymes are secreted as inactive proenzymes (zymogens).

Protein digestion is completed by the small intestinal brush border enzymes, dipeptidases, and an aminopeptidase. The main end products are amino acids (40%) and dipeptides and tripeptides (60%).

- Pancreatic enzymes are required for triglyceride, CHO, and protein digestion. Circulating CCK is almost totally responsible for their secretion following a meal.

ABSORPTION

Carbohydrate and Protein

Figure XI-1-11 illustrates the major transport processes carrying sugars and amino acids across the luminal and basal membranes of cells lining the small intestine.

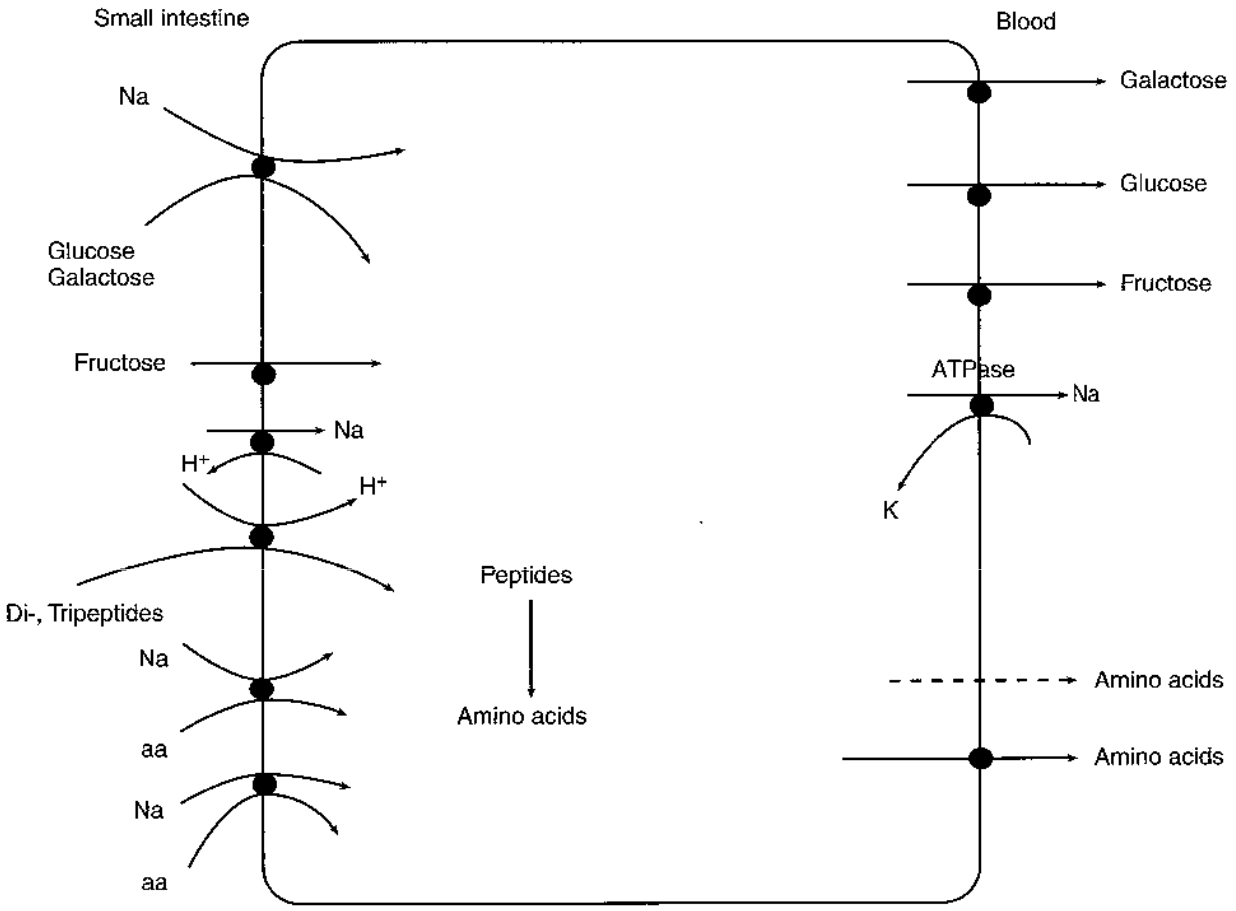


Figure XI-1-11. Absorption of Carbohydrates and Proteins

Carbohydrate

- Luminal membrane: Glucose and galactose are actively absorbed (secondary active transport linked to sodium) via the same carrier. Fructose is absorbed independently by facilitated diffusion.
- Basal membrane: The monosaccharides are absorbed passively mainly via facilitated diffusion.

Protein

- Luminal membrane: amino acids are transported by secondary active transport linked to sodium. Small peptides uptake powered by a Na-H antiporter.
- Basal membrane: simple diffusion of amino acids, although it is now known some protein-mediated transport also occurs.

Lipids

Figure XI-1-12 summarizes the digestion and absorption of lipid substances. The end products of triglyceride digestion, 2-monoglycerides and fatty acids, remain as lipid-soluble substances that are then taken up by the micelles.

Digestive products of fats found in the micelles and absorbed from the intestinal lumen may include:

- Fatty acids (long chain)
- 2-Monoglyceride
- Cholesterol
- Lysolecithin
- Vitamins A, D, E, K
- Bile salts, which stabilize the micelles

Micelles diffuse to the brush border of the intestine. The diffusion through the unstirred layer is the rate-limiting step of fat absorption.

The digested lipids then diffuse across the brush border in the lipid matrix. In the mucosal cell, triglyceride is resynthesized and forms lipid droplets (chylomicrons). These leave the intestine via the lymphatic circulation (lacteals). They then enter the bloodstream via the thoracic duct. The more water-soluble short-chain fatty acids can be absorbed by simple diffusion directly into the bloodstream. The bile salts are actively reabsorbed in the distal ileum.

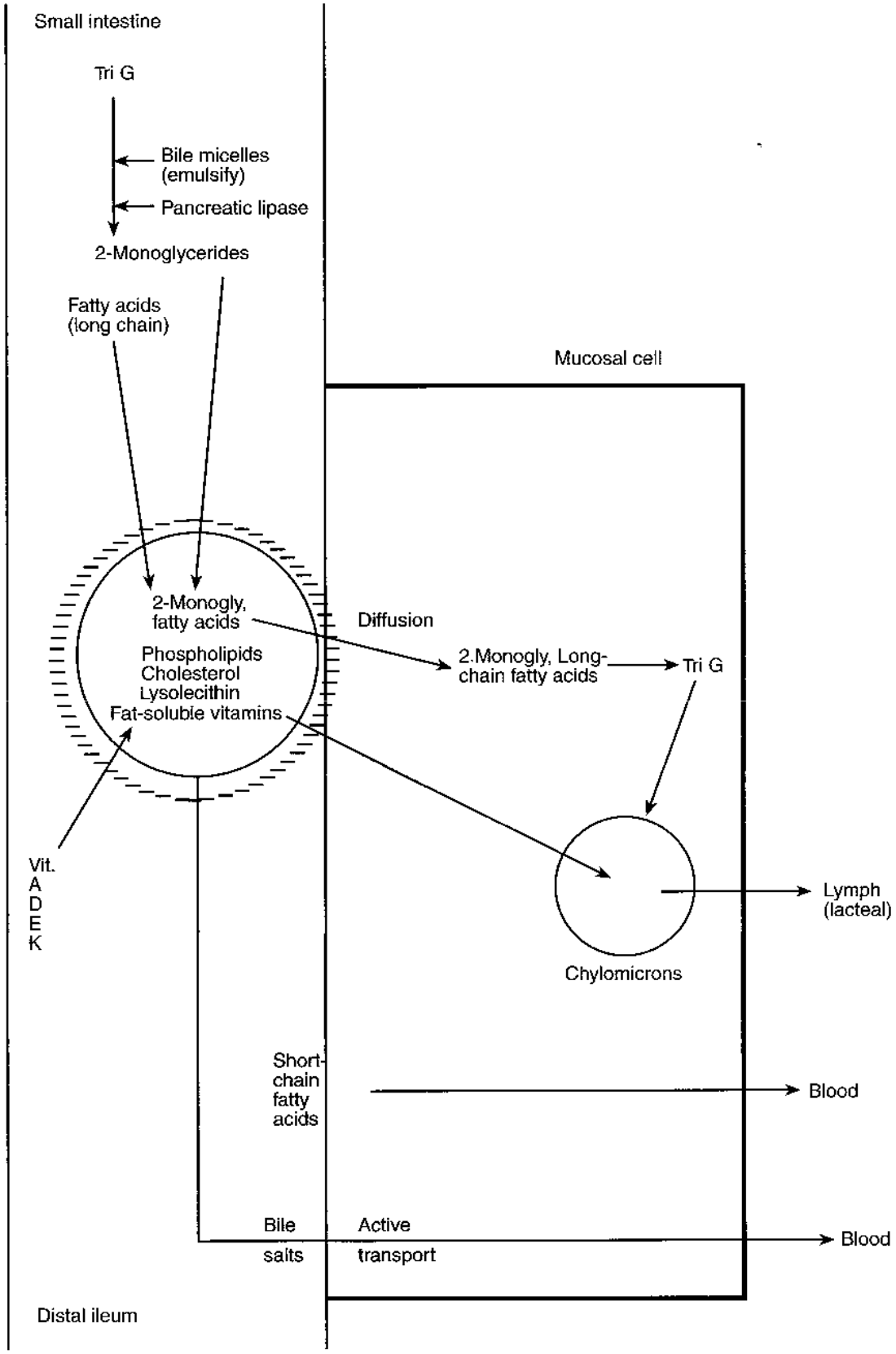


Figure XI-1-12. Absorption of Lipids

Electrolytes

The net transport of electrolytes along the length of the small and large intestine is summarized in Figure XI-1-13 and discussed in more detail below.

Duodenum

- Hypertonic fluid enters this region, and following the movement of some water into the lumen, the fluid becomes and remains isotonic.
- The absorption of most divalent ions and water-soluble vitamins begins here and continues through the small intestine.
- Injested iron and calcium tend to form insoluble salts. The acid environment of the stomach redissolves these salts, which facilitates their absorption in the small intestine. Iron and calcium absorption is diminished in individuals with a deficient stomach acid secretion.
- Iron, in the Fe^{++} form only, is absorbed mainly from the duodenum.

Jejunum

- Overall, there is a net reabsorption of water and electrolytes.
- The cellular processes involved are almost identical to those described in the renal physiology section for the cells lining the nephron proximal tubule.

Ileum

- Net reabsorption of water, sodium, chloride, and potassium continues, but there begins a net secretion of bicarbonate.
- It is in the distal ileum, and only in the distal ileum, where the reabsorption of bile salts and intrinsic factor with vitamin B_{12} takes place.

Colon

- The colon does not have digestive enzymes or the protein transporters to absorb the products of carbohydrate and protein digestion.
- Also, because bile salts are reabsorbed in the distal ileum, very few lipid-soluble substances are absorbed in the colon.
- There is a net reabsorption of water and sodium chloride, but there are limitations.
- Most of the water and electrolytes must be reabsorbed in the small intestine, or the colon becomes overwhelmed.
- Most of the water and electrolytes are absorbed in the ascending and transverse colon; thereafter, the colon has mainly a storage function.
- The colon is a target for aldosterone, where it increases sodium and water reabsorption and potassium secretion.
- Because there is a net secretion of bicarbonate and potassium, diarrhea usually produces a metabolic acidosis and hypokalemia. It commonly presents as hyperchloremic, nonanion gap metabolic acidosis, as described in the acid-base section.

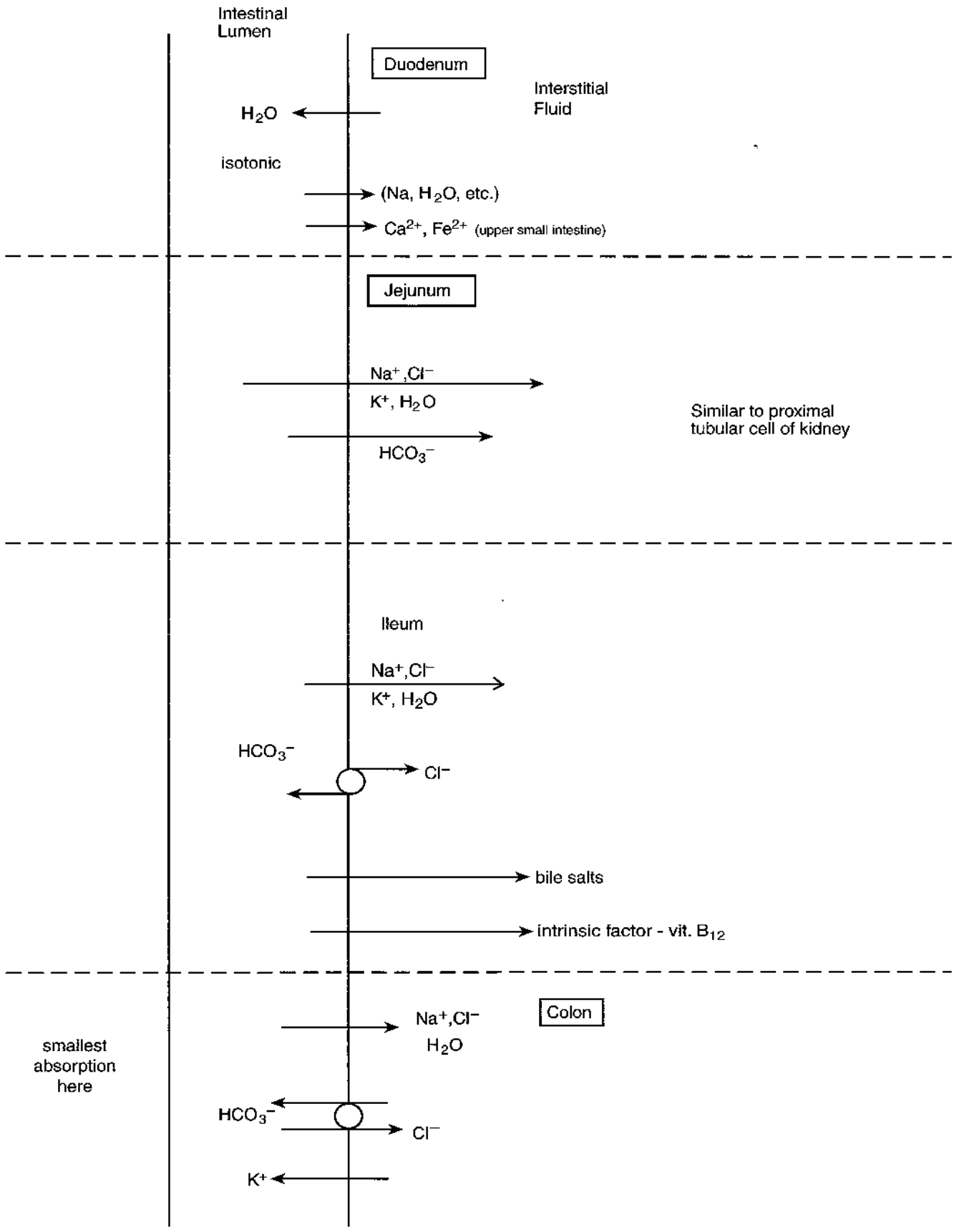


Figure XI-1-13. Transport of Electrolytes

DIARRHEA

There are many ways to classify the various diarrheas; the following is one such way. Diarrhea is, for the most part, a loss of isotonic fluid that is high in bicarbonate and potassium.

Secretory diarrhea: Any oversecretion of fluid and electrolytes can overwhelm the reabsorptive capacity of the gastrointestinal tract. It generally persists during fasting; a good example is that created by cholera toxins.

Malabsorptive diarrhea: Created by an improper absorption of nutrients, creating an osmotic effect and the retention of water and electrolytes in the lumen. It generally abates during fasting and typical examples are celiac disease (allergic reaction to gluten, which damages the villi) and lactose intolerance.

Executive disease: The mucosal distruction causes the output of a purulent bloody stool that is maintained during fasting.

Hyperactivity of the intestine: Accelerated movement of contents from the small intestine to the colon at a rate faster than they can be reabsorbed, as in inflammatory bowel disease.

Chapter Summary

* Sympathetic activity slows processes in the GI tract, whereas parasympathetic does the opposite.
* Secretin is required for releasing pancreatic bicarbonate, which neutralizes stomach acid entering the duodenum.
* CCK is required to release pancreatic enzymes and for the release of bile into the duodenum.
* Gastric stomach activity and its secretion is inhibited by stomach acid.
* Because of regional pacemaker activity, there is always some basal motor activity in the GI tract.
* Swallowing and defecation are reflexes requiring the central nervous system. Relaxation of the lower esophageal sphincter is due to the release of the inhibitory transmitter VIP.
* Following a meal, local distension and parasympathetic activity increase stomach motility. An overload of the duodenum decreases stomach motility.
* There are mixing and propulsive movements in the small intestine and colon.
* Salivary secretions are regulated via parasympathetic input. The reabsorption of sodium chloride produces a fluid that is hypotonic.
* Gastric acid secretion via a hydrogen/potassium-ATPase pump is stimulated by acetylcholine, histamine, and gastrin. A low stomach pH and a duodenal overload inhibit acid secretion.
* Pancreatic enzymes are required for the digestion of carbohydrate, protein, and lipids.
* Pancreatic fluid high in bicarbonate is required to neutralize acid entering the duodenum.
* Bile salts form micelles that are required for the digestion and absorption of lipids. Only in the distal ileum can they be actively reabsorbed. They must be recycled because the liver has a limited ability for their synthesis.
* Bile pigments are water-soluble compounds excreted via the bile and intestine.
* Electrolytes and water, but not bile pigments or bile salts, can be absorbed from the gall bladder lumen.
* Digestion of lipid requires bile micelles and pancreatic lipases. End products absorbed include 2-monoglycerides and fatty acids.
* Digestion of carbohydrate requires pancreatic amylases and the small intestinal brush border enzymes. End products absorbed will be the monosaccharides. Disaccharides cannot be absorbed from the small intestine.
* Digestion of protein requires the pancreatic proteases, which must be initially activated by enterokinase/enteropeptidase and the intestinal brush-border enzymes.
* End products absorbed include amino acids and very small peptides.
* Absorption of carbohydrate, amino acids, and small peptides is mainly by secondary active transport at the luminal membrane in the small intestine.
* Lipids are absorbed by diffusion via micelles; the chylomicrons formed in mucosal cells enter the lymphatics.

(Continued)

Chapter Summary (*Cont'd*)

* Most of the water and electrolytes are reabsorbed in the small intestine. The distal ileum reabsorbs the bile salts and intrinsic factor–vitamin B_{12} complex.
* The colon does not have digestive enzymes or the transporters to absorb the end products of digestion.
* The colon has a net absorption of water and electrolytes, which is influenced by aldosterone but has a net secretion of bicarbonate and potassium.
* Diarrhea is the loss of isotonic fluid, which is high in bicarbonate and potassium.

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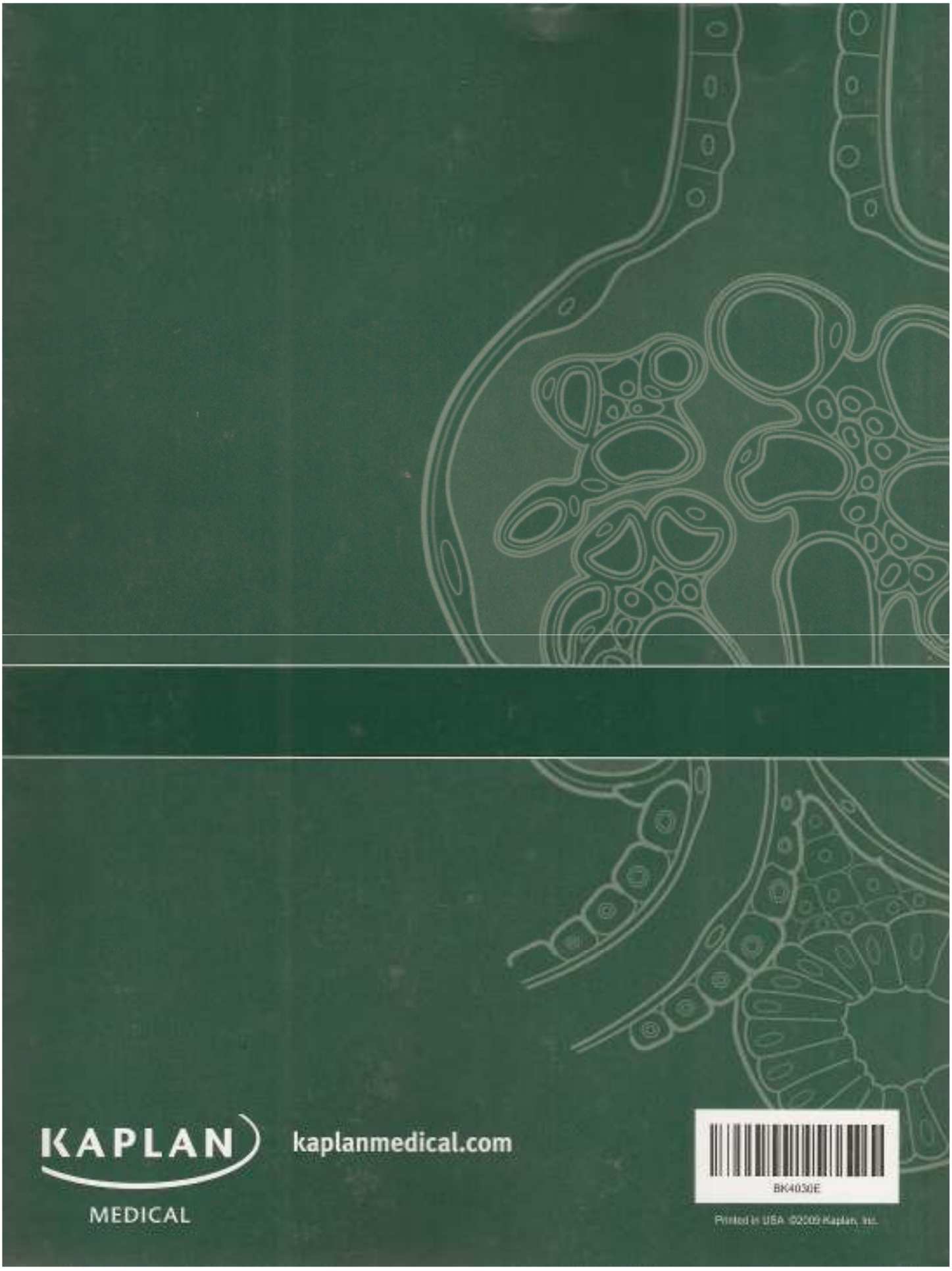

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