REGULATION OF ARTERIAL BLOOD PRESSURE

- **Blood pressure -** the force exerted by the blood against any unit area of the vessel wall.
  - When one says that pressure in a vessel is 50 mmHg, one means that the force exerted is sufficient to push a column of mercury against gravity up to a level 50 mm high.
- **Systolic pressure-** is the highest arterial pressure during a cardiac cycle.
  - This occurs when the heart contracts and blood is ejected into the arterial system.
- **Diastolic pressure-** is the lowest arterial pressure during a cardiac cycle.
  - This occurs when the heart is relaxed and blood is being returned to the heart via the veins.
- **Mean arterial pressure-** The mean arterial pressure is the average of the arterial pressures measured millisecond by millisecond over a period of time.
  - It is not equal to the average of the systolic and diastolic pressures because at normal heart rates, a greater fraction of the cardiac cycle is spent in diastole than in systole. Thus, the arterial pressure remains closer to diastolic pressure than to systolic pressure during the greater part of the cardiac cycle.
  - At the usual heart rate, the mean arterial pressure is determined about 60% by the diastolic pressure and 40% by the systolic pressure.

$$Mean\ Arterial\ Pressure = DP + \frac{1}{3}(SP - DP)$$

$$MAP = DP + \frac{(SP-DP)}{3} \rightarrow \frac{3DP+SP-DP}{3} \rightarrow \boldsymbol{Mean\ Arterial\ Pressure} = \frac{\boldsymbol{2DP+SP}}{3}$$

  - Nearer the diastolic pressure than to the systolic pressure during the greater part of the cardiac cycle.
- **Pulse pressure-** is the difference between systolic and diastolic pressures, which is about 40 mmHg.
  - Factors that affect pulse pressure:
    1. The **stroke volume output** of the heart
    2. The **compliance (total distensibility)** of the arterial tree
    3. The **character of ejection** from the heart during systole.
    - The first two are major factors while the third is a less important factor.
  - However, the most important determinant of pulse pressure is **stroke volume**.
    - As blood is ejected from the left ventricle into the arterial system, systolic pressure increases dramatically because of the relatively low capacitance of the arteries.
    - Since diastolic pressure remains unchanged during ventricular systole, the pulse pressure increases to the same extent as does systolic pressure.
  - Decreases in capacitance, such as those that occur with the aging process, cause the pulse pressure to increase.
- **Characteristics of the pulse** and **Proper technique of taking the pulse in various peripheral areas** (refer to CASE 3)
- **Proper technique in taking the blood pressure**
  - **Palpatory method**
    - The systolic pressure can be determined by inflating an arm cuff and then letting the pressure fall and determining the pressure at which the radial pulse first becomes palpable.
    - The pressures obtained by this method are usually 2-5 mmHg lower than those measured by the auscultatory method.
  - **Auscultatory method**
    - An inflatable cuff attached to a mercury monometer (**sphygmomanometer**) is wrapped around the arm and a stethoscope is placed over the brachial artery at the elbow.
    - When the cuff pressure is great enough to close the artery during part of the arterial pressure cycle, a sound is heard with each pulsation. These sounds are called **Korotkoff sounds**, which are believed to be caused mainly by blood jetting through the partly occluded vessel (turbulent flow in the brachial artery).
    - The cuff pressure at which the sounds are first heard is the **systolic pressure**. The **diastolic pressure** correlates best with the pressure at which the sound disappears.
    - More sensitive and more precise method for measuring systolic pressure.
    - Also permits the diastolic pressure to be estimated.
- **Normal blood pressure range for adults according to JNC 8**
  - The blood pressure in the brachial artery in young adults in the sitting or lying position at rest is approximately < 120/80 mmHg.
    - Systolic BP: **< 120 mmHg**
    - Diastolic BP: **< 80 mmHg**

Blood Pressure Classification for Adults—JNC 7, American Society of Hypertension

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	<120	<80
Prehypertension	120–139	80–89
Stage 1 hypertension		
Age ≥18 to <60 yrs	140–159	90–99
Age ≥60 yrs[a]	150–159	90–99
Stage 2 hypertension	≥160	≥100
If diabetes or renal disease (including age ≥60 yrs)	<140	<90

[a]The American Society of Hypertension raises this cutoff to age ≥80 years.

Sources: Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens.* 2014;16:14; Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure—The JNC 7 Report. *JAMA.* 2003;289:2560. Available at http://www.nhlbi.nih.gov/health-pro/guidelines/current/

Age ≥60 years	Systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg (strong recommendation)
Age <60 years	Systolic blood pressure ≥140 mm Hg (expert opinion) Diastolic blood pressure ≥90 mm Hg (strong recommendation)
Age >18 years with chronic kidney disease or diabetes	Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (expert opinion)

Source: James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311:507.

- **BP Classification for Adult Filipinos**

TABLE 1 Blood pressure classification for adult filipinos

Category	Blood pressure range
Normal BP	< 120/80 mm Hg
Borderline BP	120–139/ 80–89 mm Hg
Hypertension	≥140/90 mm Hg

- **Limitations of BP reading**
  - **Cuffs that are too short or too narrow** may give falsely high readings.
    - Using a regular-size cuff on an obese arm may lead to a false diagnosis of hypertension.
    - A loose cuff or a bladder that balloons outside the cuff leads to falsely high readings.
  - **Position of the arm is below the mid chest level** so the brachial artery is below heart level resulting in a falsely high blood pressure.
    - The patient's own effort to support the arm may raise the blood pressure.
  - An **unrecognized auscultatory gap** may lead to serious underestimation of systolic pressure or overestimation of diastolic pressure.
- **Effects of changes in cardiac output and total peripheral resistance on arterial blood pressure and pulse pressure**
  - Normal total peripheral resistance (TPR) = Normal cardiac output (CO)
    - ↑**TPR =** ↓CO.
    - ↓**TPR =** ↑CO, ↑↓ pulse pressure, ↓ arterial pressure
    - ↓**CO =** ↓arterial pressure
- **Effect of the following physiologic factors on the blood pressure:**
  - **Age**
    - In apparently healthy humans, both the systolic and the diastolic pressures increase with age.
    - An important cause of the systolic pressure rise is decreased distensibility of the arteries; at the same level of cardiac output, the systolic pressure is higher in old subjects than in young ones because there is less increase in the volume of the arterial system during systole to accommodate the same amount of blood.
  - **Emotion**
    - Increases the cardiac output and it may be difficult to obtain a truly resting blood pressure in an excited or tense individual.
    - Because of nervousness, about 20% of hypertensive patients have higher blood pressure in the doctor's office than during their normal daytime activity (white coat hypertension).
  - **Exercise**
    - The same brain activity that sends motor signals to the peripheral muscles to exercise also sends simultaneous signals into the autonomic nervous centers of the brain to excite circulatory activity, causing venous constriction, increased heart rate, and increased contractility of the heart; all these changes acting together increase the arterial pressure even above normal which in turn forces more blood flow through the active muscles.
  - **Body position (posture)**
    - Changes in gravitational forces
    - The following changes occur when an individual moves from a supine position to a standing position:

1. **When a person stands**, a significant volume of blood pools in the lower extremities because of the high compliance of the veins. (Muscular activity would prevent this pooling.)
2. **As a result of venous pooling** and **increased local venous pressure**, capillary hydrostatic pressure (Pc) in the legs increases and fluid is filtered into the interstitium. If net filtration of fluid exceeds the ability of the lymphatics to return it to the circulation, edema will occur.
3. **Venous return decreases.** As a result of the decrease in venous return, both stroke volume and cardiac output decrease (Frank-Starling relationship).
4. **Initially, arterial pressure decreases** because of the reduction in cardiac output. If cerebral blood pressure becomes low enough, fainting may occur.
5. **Compensatory mechanisms** will attempt to increase blood pressure to normal.
   - The **carotid sinus baroreceptors** respond to the decrease in arterial pressure by decreasing the firing rate of the carotid sinus nerves.
   - A coordinated response from the **vasomotor center** then increases sympathetic outflow to the heart and blood vessels and decreases parasympathetic outflow to the heart.
   - As a result, heart rate, contractility, TPR, and venous return increase, and blood pressure increases toward normal.
6. **Orthostatic hypotension** (fainting or light-headedness on standing) may occur in individuals whose baroreceptor reflex mechanism is impaired (e.g., individuals treated with sympatholytic agents) or who are volume depleted

table 3.4 Summary of Responses to Standing

Parameter	Initial Response to Standing	Compensatory Response
Arterial blood pressure	↓	↑ (toward normal)
Heart rate	—	↑
Cardiac output	↓	↑ (toward normal)
Stroke volume	↓	↑ (toward normal)
TPR	—	↑
Central venous pressure	↓	↑ (toward normal)

TPR = total peripheral resistance.

- **Mechanisms involved in the regulation of blood pressure in reference to:**
  - **Neural control**
    - The most important mechanisms for regulating arterial pressure are a fast, neurally-mediated baroreceptor mechanism and a slower, hormonally regulated renin-angiotensin-aldosterone mechanism.
    - **Baroreceptor reflex**
      - Includes **fast, neural mechanisms.**
      - Is a negative feedback system that is responsible for the minute-to-minute regulation of arterial blood pressure.
      - Baroreceptors are stretch receptors located within the walls of the carotid sinus near the bifurcation of the common carotid arteries.
      - Steps in the baroreceptor reflex (Figure 3.16)
        1. A **decrease in arterial pressure** decreases stretch on the walls of the carotid sinus.
           - ✓ Because the baroreceptors are most sensitive to **changes in arterial pressure**, rapidly decreasing arterial pressure produces the greatest response.
           - ✓ Additional baroreceptors in the **aortic arch** respond to increases, but not to decreases, in arterial pressure.

2. Decreased stretch **decreases the firing rate of the carotid sinus nerve** [Hering nerve, cranial nerve (CN) IX], which carries information to the vasomotor center in the brainstem.
3. The **set point for mean arterial pressure** in the vasomotor center is about 100 mm Hg. Therefore, if mean arterial pressure is less than 100 mm Hg, a series of autonomic responses is coordinated by the vasomotor center. These changes will attempt to increase blood pressure toward normal.
4. The **responses of the vasomotor center** to a decrease in mean arterial blood pressure are coordinated to increase the arterial pressure back to 100 mm Hg. The responses are **decreased parasympathetic (vagal) outflow to the heart and increased sympathetic outflow to the heart and blood vessels.**
   - ❖ The following four effects attempt to increase the arterial pressure back toward normal:
     - ➢ ↑**heart rate**, resulting from decreased parasympathetic tone and increased sympathetic tone to the SA node of the heart.
     - ➢ ↑**contractility and stroke volume**, resulting from increased sympathetic tone to the heart.
       - ✓ Together with the increase in heart rate, the increases in contractility and stroke volume produce an increase in cardiac output that increases arterial pressure.
     - ➢ ↑**vasoconstriction of arterioles**, resulting from the increased sympathetic outflow. As a result, TPR and arterial pressure will increase.
     - ➢ ↑**vasoconstriction of veins (venoconstriction)**, resulting from the increased sympathetic outflow. Constriction of the veins causes a decrease in unstressed volume and an increase in venous return to the heart. The increase in venous return causes an increase in cardiac output by the Frank-Starling mechanism.

   - ❖ Example of baroreceptor reflex: response to **acute blood loss**

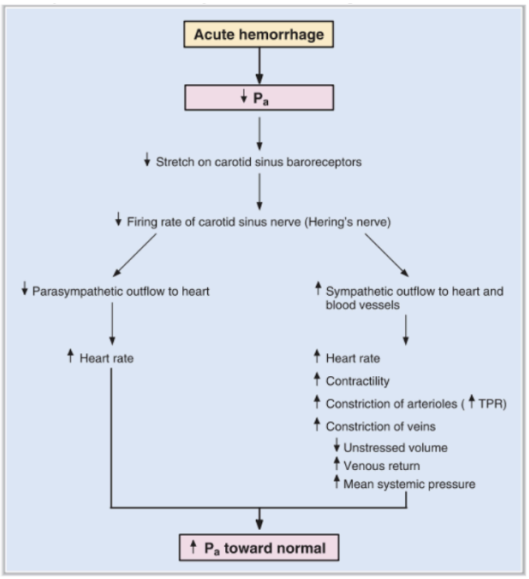

FIGURE 3.16. Role of the baroreceptor reflex in the cardiovascular response to hemorrhage. P_a = mean arterial pressure; TPR = total peripheral resistance.

   - ❖ Example of the baroreceptor mechanism: **Valsalva maneuver**
     - ➢ The integrity of the baroreceptor mechanism can be tested with the Valsalva maneuver (i.e., expiring against a closed glottis).
     - ➢ Expiring against a closed glottis causes an increase in intrathoracic pressure, which decreases venous return.
     - ➢ The decrease in venous return causes a decrease in cardiac output and arterial pressure (Pa).
     - ➢ If the baroreceptor reflex is intact, the decrease in Pa is sensed by the baroreceptors, leading to an increase in sympathetic outflow to the heart and blood vessels. In the test, an increase in heart rate would be noted.
     - ➢ When the person stops the maneuver, there is a rebound increase in venous return, cardiac output, and Pa. The increase in Pa is sensed by the baroreceptors, which direct a decrease in heart rate.

- ○ **Hormonal control including autocoids**
  - ■ **Renin-angiotensin-aldosterone system**
    - ❖ Is a slow, hormonal mechanism.
    - ❖ Is used in long-term blood pressure regulation by adjustment of blood volume.
    - ❖ **Renin** is an enzyme. **Angiotensin I** is inactive.
    - ❖ **Angiotensin II** is physiologically active.
    - ❖ **Angiotensin II** is degraded by **angiotensinase**. One of the peptide fragments, **angiotensin III**, has some of the biologic activity of angiotensin II.
    - ❖ **Steps in the renin-angiotensin-aldosterone system**
      1. A **decrease in renal perfusion pressure** causes the **juxtaglomerular cells** of the afferent arteriole to secrete **renin**.
      2. Renin is an enzyme that catalyzes the conversion of angiotensinogen to **angiotensin I** in **plasma**.
      3. **Angiotensin-converting enzyme (ACE)** catalyzes the conversion of angiotensin I to **angiotensin II**, primarily in the **lungs**.
      - ➢ **ACE inhibitors** (e.g., captopril) block the conversion of angiotensin I to angiotensin II and, therefore, decrease blood pressure.
      - ➢ **Angiotensin receptor (AT1) antagonists** (e.g., losartan) block the action of angiotensin II at its receptor and decrease blood pressure.
      4. **Angiotensin II** has 4 effects:
      - ➢ It stimulates the synthesis and secretion of aldosterone by the adrenal cortex.
        - ★ Aldosterone increases **Na+ reabsorption** by the renal distal tubule, thereby increasing extracellular fluid (ECF) volume, blood volume, and arterial pressure.
        - ★ This action of aldosterone is **slow** because it requires new protein synthesis.
      - ➢ It increases **Na+-H+ exchange** in the proximal convoluted tubule.
        - ★ This action of angiotensin II directly increases Na+ reabsorption, complementing the indirect stimulation of Na+ reabsorption via aldosterone.
        - ★ This action of angiotensin II leads to contraction alkalosis.
      - ➢ It **increases thirst** and therefore water intake
      - ➢ It causes **vasoconstriction of the arterioles**, thereby increasing TPR and arterial pressure.
    - ❖ Example: **response of the renin-angiotensin-aldosterone system to acute blood loss**

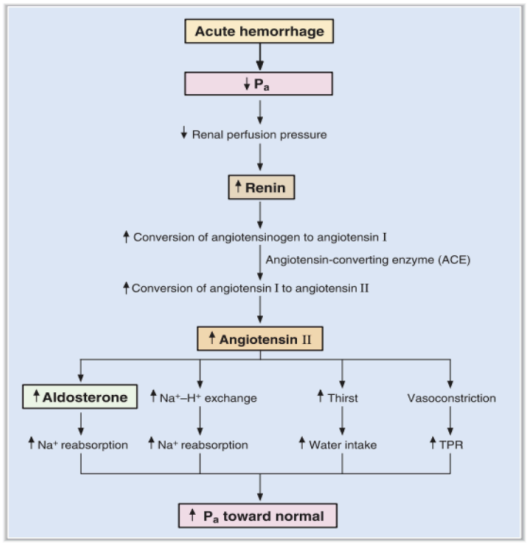

FIGURE 3.17. Role of the renin–angiotensin–aldosterone system in the cardiovascular response to hemorrhage. P_a = mean arterial pressure; TPR = total peripheral resistance.

- **Autoregulation or local control**
  - Cerebral ischemia
    - When the brain is ischemic, the partial pressure of carbon dioxide (Pco2) in brain tissue increases.
    - Chemoreceptors in the vasomotor center respond by **increasing sympathetic outflow** to the heart and blood vessels.
      - Constriction of arterioles causes intense **peripheral vasoconstriction** and increased TPR. Blood flow to other organs (e.g., kidneys) is significantly reduced in an attempt to preserve blood flow to the brain.
      - **Mean arterial pressure** can increase to life-threatening levels.
    - The **Cushing reaction** is an example of the response to cerebral ischemia. Increases in intracranial pressure cause compression of the cerebral blood vessels, leading to cerebral ischemia and increased cerebral Pco2. The vasomotor center directs an increase in sympathetic outflow to the heart and blood vessels, which causes a profound increase in arterial pressure.
  - **Chemoreceptors in the carotid and aortic bodies**
    - Are located near the bifurcation of the common carotid arteries and along the aortic arch.
    - Have very high rates of O2 consumption and are very sensitive to decreases in the partial pressure of oxygen (Po2).
    - **Decreases in Po_2** activate vasomotor centers that produce vasoconstriction, an increase in TPR, and an increase in arterial pressure.
  - **Vasopressin [antidiuretic hormone (ADH)]**
    - Is involved in the regulation of blood pressure in response to hemorrhage, but not in minute-to-minute regulation of normal blood pressure.
    - Atrial receptors respond to a decrease in blood volume (or blood pressure) and cause the release of vasopressin from the posterior pituitary.
    - Vasopressin has two effects that tend to increase blood pressure toward normal:
      - It is a **potent vasoconstrictor** that increases TPR by activating **V_1 receptors** on the arterioles.
      - It **increases water reabsorption** by the renal distal tubule and collecting ducts by activating **V_2 receptors**.
  - **Atrial natriuretic peptide (ANP)**
    - Is released from the atria in response to an increase in blood volume and atrial pressure.
    - Causes **relaxation of vascular smooth muscle**, dilation of arterioles, and decreased TPR.
    - Causes **increased excretion of Na+ and water** by the kidney, which reduces blood volume and attempts to bring arterial pressure down to normal.
    - Inhibits **renin secretion**.

CASE 4
VENOUS PRESSURE AND FLOW

Definition of Terms

Central venous pressure (Right atrial pressure)
- Pressure in the right atrium

Peripheral venous pressure
- Pressure in the peripheral veins

Mean circulatory filling pressure
- Without blood flow, the pressures everywhere in the circulation become equal after a minute or so. This equilibrated pressure level is called mean circulatory filling pressure.

Venous return
- The quantity of blood flowing from the veins into the right atrium each minute.

Methods for Measuring Venous Pressure

- **Clinical Estimation of Venous Pressure**
  - Venous pressure can be estimated by simply observing the degree of distention of the peripheral veins, especially of the neck veins.
  - For example, in the sitting position, the neck veins are never distended in the normal, quietly resting person. However, when the right atrial pressure increases to as much as +10 mm Hg, the lower veins of the neck begin to protrude and, at +15 mm Hg atrial pressure, all the veins in the neck become distended.
- **Direct Measurement of Venous Pressure and Right Atrial Pressure**
  - Venous pressure can be measured easily by inserting a needle directly into a vein and connecting it to a pressure recorder.
  - The only means whereby right atrial pressure can be measured accurately is by inserting a catheter through the peripheral veins and into the right atrium. Pressures measured through such central venous catheters are often used in some types of hospitalized cardiac patients to provide a constant assessment of the heart-pumping ability.

Principle regarding Venous Pressure and Flow

- Blood from all the systemic veins flows into the **right atrium.** Therefore, the pressure in the right atrium is called the **central venous pressure**.
- **Right atrial pressure** is regulated by a balance between (1) the ability of the heart to pump blood out of the right atrium and ventricle into the lungs and (2) the tendency for blood to flow from the peripheral veins into the right atrium.
- If the right heart is pumping strongly, the right atrial pressure decreases. Conversely, weakness of the heart elevates the right atrial pressure. Any effect that causes rapid inflow of blood into the right atrium from the peripheral veins elevates the right atrial pressure.
- **Factors that can increase venous return and thereby increase the right atrial pressure are as follows:**
  - Increased blood volume
  - Increased large vessel tone throughout the body with resultant
  - increased peripheral venous pressures
  - Dilation of the arterioles, which decreases the peripheral resistance and allows rapid flow of blood from the arteries into the veins.
  - Positive pressure breathing
  - Straining
  - Heart failure
- **Factors that decrease central venous pressure (right atrial pressure):**
  - Negative pressure breathing
  - Shock
- The same factors that regulate right atrial pressure also contribute to the regulation of cardiac output because the amount of blood pumped by the heart depends on both the ability of the heart to pump and the tendency for blood to flow into the heart from the peripheral vessels.
- The normal right atrial pressure is about **0 mm Hg**, which is equal to the atmospheric pressure around the body. It can increase to **20 to 30 mm Hg** under very abnormal conditions, such as the following: (1) serious heart failure; or (2) after massive transfusion of blood, which greatly increases the total blood volume and causes excessive quantities of blood to attempt to flow into the heart from the peripheral vessels.
- The lower limit to the right atrial pressure is usually about **-3 to -5 mmHg** below atmospheric pressure, which is also the pressure in the chest cavity that surrounds the heart. The right atrial pressure approaches these low values when the heart pumps with exceptional vigor or when blood flow into the heart from the peripheral vessels is greatly depressed, such as after severe hemorrhage.

Effects of the following on venous pressure and flow

- **Venous resistance to flow**
  - Large veins have so little resistance to blood flow when they are distended that the resistance then is almost zero.
  - However, most of the large veins that enter the thorax are compressed at many points by the surrounding tissues, so that blood flow is impeded at these points. For example, the veins from the arms are compressed by their sharp angulations over the first rib. Also, the pressure in the neck veins often falls so low that the atmospheric pressure on the outside of the neck causes these veins to collapse. Finally, veins coursing through the abdomen are often compressed by different organs and by the intra-abdominal pressure, so they usually are at least partially collapsed to an ovoid or slit-like state. For these reasons, the large veins do usually offer some resistance to blood flow, and thus the pressure in the more peripheral small veins in a person lying down is usually +4 to +6 mmHg greater than the right atrial pressure.
- **Factors that tend to collapse the veins entering the thorax:**
  - Atmospheric pressure collapse in neck
  - Rib collapse
  - Axillary collapse
  - Intrathoracic pressure = -4 mm Hg
  - Abdominal pressure collapse

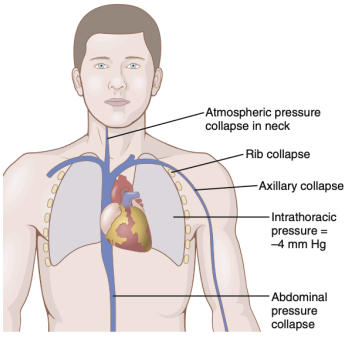

Figure 15-9. Compression points that tend to collapse the veins entering the thorax.

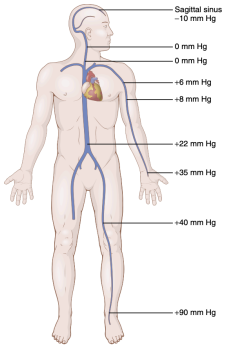

Figure 15-10. Effect of gravitational pressure on the venous pressures throughout the body in the standing person.

- **Posture**
  - Gravitational pressure also occurs in the vascular system because of the weight of the blood in the vessels.

- When a person is **standing**, the pressure in the right atrium remains about **0 mm Hg** because the heart pumps any excess blood that attempts to accumulate at this point into the arteries. However, in an adult who is standing absolutely still, the pressure in the **veins of the feet** is about **+90 mm Hg** simply because of the gravitational weight of the blood in the veins between the heart and the feet. The venous pressures at other levels of the body are proportionately between 0 and 90 mm Hg.
- In the **arm veins**, the pressure at the level of the top rib is usually about **+6 mm Hg** because of compression of the subclavian vein as it passes over this rib.
  - The gravitational pressure down the length of the arm is then determined by the distance below the level of this rib. Thus, if the gravitational difference between the level of the rib and the hand is +29 mm Hg, this gravitational pressure is added to the +6 mm Hg pressure caused by compression of the vein as it crosses the rib, making a total of +35 mm Hg pressure in the veins of the hand.
- The **neck veins** of a person standing upright collapse almost completely all the way to the skull because of atmospheric pressure on the outside of the neck. This collapse causes the pressure in these veins to remain at **zero** along their entire extent.
  - Any tendency for the pressure to rise above this level opens the veins and allows the pressure to fall back to zero because of flow of the blood.
  - Conversely, any tendency for the neck vein pressure to fall below zero collapses the veins still more, which further increases their resistance and again returns the pressure back to zero.
- The **veins inside the skull**, on the other hand, are in a chamber (the skull cavity) that cannot collapse. Consequently, negative pressure can exist in the dural sinuses of the head; in the standing position, the venous pressure in the sagittal sinus at the top of the brain is about **-10 mmHg** because of the hydrostatic “suction” between the top of the skull and the base of the skull.
  - Therefore, if the sagittal sinus is opened during surgery, air can be sucked immediately into the venous system; the air may even pass downward to cause air embolism in the heart and death.

- **Cardiac Contraction**
  - Atrial pressure drops sharply during the ejection phase of the ventricular systole because the atrioventricular valves are pulled downward, increasing the capacity of the atria.
    - This action sucks blood into the atria from the great veins.
    - The sucking of the blood into the atria during systole contributes appreciably to the venous return, especially at rapid heart rates.
  - Close to the heart, venous flow becomes pulsatile.
    - When the heart rate is slow, two periods of peak flow are detectable, one during **ventricular systole**, due to pulling down of the atrioventricular valves, and one in **early diastole**, during the period of rapid ventricular filling.
- **Thoraco-Abdominal Pump (Respiratory Pump)**
  - The respiratory pump works in the following manner:
    - When you inhale, the diaphragm is pulled downward and the rib cage expands, which lowers pressure in the thoracic cavity and raises pressure in the abdominal cavity.
      - This action creates a pressure gradient that promotes movement of blood from abdominal veins to the central veins located in the thoracic cavity. The drop in venous pressure during inspiration aids venous return.
    - When you exhale, the thoracic pressure rises and abdominal pressure falls.
      - This creates a pressure gradient that would tend to favor the backward movement of blood from the central veins to the abdominal veins, but such backward flow is prevented by the closure of the valves in the abdominal veins.
      - Instead, the rise in thoracic pressure drives the forward movement of blood from the central veins to the heart, thereby, promoting increased end-diastolic volume and cardiac output.
  - Skeletal muscle pump (Venous pump)
    - The peripheral veins contain one-way valves that allow blood to flow forward the heart but prevent it from flowing backward.
    - When skeletal muscles contract, they press against veins traveling between them, which raises the pressure of blood within them. This increased pressure forces the more distal valves to close, preventing blood from flowing backward, and forces the more proximal valves to open, allowing blood to flow toward the heart.
    - When the muscles relax and the pressure drops, backflow is prevented by closure of one-way valves in the veins.
    - By alternately contracting and relaxing, muscles act as “pumps” or “auxiliary hearts” that help drive blood toward the central veins, which raises central venous pressure.
      - For this reason, any exercise that involves rhythmic muscle contractions, such as walking, or running, promotes an increase in venous return, increased stroke volume, and increased cardiac output.
  - Venomotor tone
  - The activity of vasoconstrictor neurons of the sympathetic nervous system triggers increased contractile activity in venous smooth muscle, with a resulting rise in tension referred to as venomotor tone.
  - An increase in venomotor tone has two effects:
    - Constriction of veins raises the pressure of blood within them, which forces blood to return to the heart and briefly increases stroke volume.
    - Increased wall tension reduces venous compliance which raises central venous pressure and produces a sustained increase in stroke volume.
  - Therefore, an increase in venomotor tone promotes a rise in cardiac output and mean arterial pressure. Changes in venomotor tone are important components of the reflexes that regulate arterial pressure.
- Venous valves
  - Were it not for valves in the veins, the gravitational pressure effect would cause the venous pressure in the feet to always be about +90 mm Hg in a standing adult.
    - However, every time the legs move, the muscles tighten and compress the veins in or adjacent to the muscles, which squeezes the blood out of the veins.
    - However, the valves in the veins are arranged so that the direction of venous blood flow can only be toward the heart.
    - Consequently, every time a person moves the legs or even tenses the leg muscles, a certain amount of

venous blood is propelled toward the heart. This pumping system is known as the venous pump or muscle pump, and it is efficient enough that under ordinary circumstances, the venous pressure in the feet of a walking adult remains less than +20 mm Hg.

- The valves of the venous system may become "incompetent" or even be destroyed when the veins have been overstretched by excess venous pressure lasting weeks or months, which can occur in pregnancy or when a person stands most of the time.
- Stretching the veins increases their cross-sectional areas, but the leaflets of the valves do not increase in size. Therefore, the leaflets of the valves no longer close completely.
  - With this lack of complete closure, the pressure in the veins of the legs increases greatly because of failure of the venous pump, which further increases the sizes of the veins and finally destroys the function of the valves entirely.
  - Thus, the person develops what are called varicose veins, which are characterized by large bulbous protrusions of the veins beneath the skin of the entire leg, particularly the lower leg.

Functional relationship between cardiac output and central venous pressure (right atrial pressure)

- Cardiac and vascular function curves- are simultaneous plots of cardiac output and venous return as a function of right atrial pressure or end-diastolic volume.
- The cardiac function (cardiac output) curve
  - Depicts the Frank-Starling relationship for the ventricle.
  - Is a characteristic of the heart itself.
  - Shows that cardiac output is a function of end-diastolic volume- a consequence of the length-tension relationship in cardiac muscle fibers. Remember that changes in end-diastolic volume are a major mechanism for altering cardiac output.

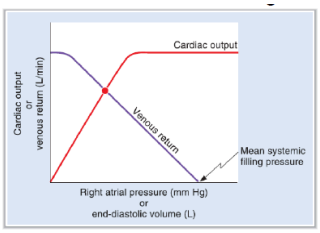

FIGURE 3.11. Simultaneous plots of the cardiac and vascular function curves. The curves cross at the equilibrium point for the cardiovascular system.

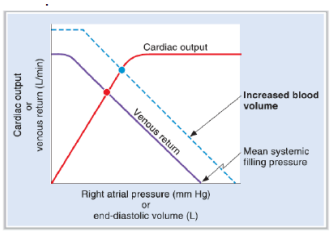

FIGURE 3.12. Effect of increased blood volume on the mean systemic filling pressure, vascular function curve, cardiac output, and right atrial pressure.

- The vascular function (venous return) curve
  - Depicts the relationship between blood flow through the vascular system (or venous return) and right atrial pressure.
  - Defines the changes in central venous pressure that are caused by changes in cardiac output.
  - Is entirely independent of the characteristics of the heart.
  - Mean systemic filling pressure
    - The point at which the vascular function curve intersects the x-axis.
    - Equals right atrial pressure when there is "no flow" in the cardiovascular system.
    - It is measured when the heart is stopped experimentally. Under these conditions, cardiac output and venous return are zero, and pressure is equal throughout the cardiovascular system.
    - When the right atrial pressure rises to equal the mean systemic filling pressure, there is no longer any pressure difference between the peripheral vessels and the right atrium. There can no longer be any flow from any peripheral vessels back to the atrium. However, when the right atrial pressure falls progressively lower than the mean systemic filling pressure, the flow to the heart increases proportionately. The greater the difference between the mean systemic filling pressure and the right atrial pressure, the greater the venous return.
    - The difference between these two pressures is called pressure gradient for venous return.
    - Mean systemic filling pressure is increased by an increase in blood volume or by a decrease in venous capacitance (where blood is shifted from the veins to the arteries).
      - An increase in mean systemic filling pressure is reflected in a shift of the vascular function curve to the right.
    - Mean systemic filling pressure is decreased by a decrease in blood volume or by an increase in venous capacitance (where blood is shifted from the arteries to the veins).
      - A decrease in mean systemic filling pressure is reflected in a shift of the vascular function curve to the left.
- Slope of the venous return curve
  - It is determined by the resistance of the arterioles.
  - A clockwise rotation of the venous return curve indicates a decrease in total peripheral resistance (TPR). When TPR is decreased for a given right atrial pressure, there is an increase in venous return (i.e., vasodilation of the arterioles "allows" more blood to flow from the arteries to the veins and back to the heart).
  - A counterclockwise rotation of the venous return curve indicates an increase in TPR. When TPR is increased for a given right atrial pressure, there is a decrease in venous return to the heart (i.e., vasoconstriction of the arterioles decreases blood flow from the arteries to the veins and back to the heart).

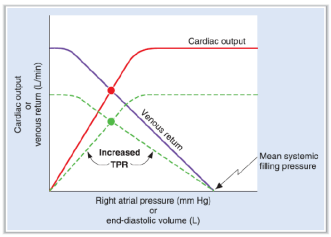

FIGURE 3.13. Effect of increased total peripheral resistance (TPR) on the cardiac and vascular function curves and on cardiac output.

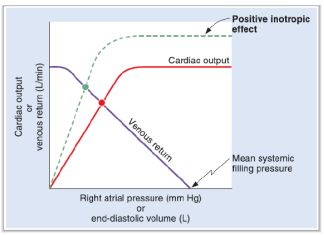

FIGURE 3.14. Effect of a positive inotropic agent on the cardiac function curve, cardiac output, and right atrial pressure.

- Combining Cardiac Output and Venous Return Curves
  - When cardiac output and venous return are simultaneously plotted as a function of right atrial pressure, they intersect at a single value of right atrial pressure.
  - The point at which the two curves intersect is the **equilibrium**, or **steady-state point**. Equilibrium occurs when cardiac output equals venous return.
  - Cardiac output can be changed by altering the cardiac output curve, the venous return curve, or both curves simultaneously. The superimposed curves can be used to predict the direction and magnitude of changes in cardiac output and the corresponding values of right atrial pressure.
  - **Inotropic agents change the cardiac output curve**
    - **Positive inotropic agents** (e.g., cardiac glycosides, digitalis) produce increased contractility and increased cardiac output.
      - The equilibrium, or intersection, point shifts to a higher cardiac output and a correspondingly lower right atrial pressure.
      - Right atrial pressure decreases because more blood is ejected from the heart on each beat (increased stroke volume).
    - **Negative inotropic agents** produce decreased contractility and decreased cardiac output.
  - Changes in blood volume or venous capacitance change the venous return curve

- **Increases in blood volume** or **decreases in venous capacitance** increase mean systemic filling pressure, shifting the venous return curve to the right in a parallel fashion. A new equilibrium, or intersection point is established at which both **cardiac output** and **right atrial pressure** are **increased**.
- **Decreases in blood volume** (e.g., hemorrhage) or **increases in venous capacitance** have the opposite effect- decreased mean systemic filling pressure and a shift of the venous return curve to the left in a parallel fashion. A new equilibrium point is established at which both **cardiac output** and **right atrial pressure** are **decreased**.

- **Changes in TPR change both the cardiac output and the venous return curves.**
  - Changes in TPR alter both curves simultaneously; therefore, the responses are more complicated than those noted in the previous examples.
  - **Increasing TPR** causes a **decrease** in both **cardiac output** and **venous return**.
    - A **counterclockwise rotation of the venous return curve** occurs. Increased TPR results in decreased venous return as blood is retained on the arterial side.
    - A **downward shift of the cardiac output curve** is caused by the increased aortic pressure (increased afterload) as the heart pumps against a higher pressure.
    - As a result of these simultaneous changes, a new equilibrium point is established at which both **cardiac output** and **venous return** are **decreased**, but right atrial pressure is unchanged.
  - **Decreasing TPR** causes an **increase** in both **cardiac output** and **venous return**.
    - A **clockwise rotation of the venous return curve** occurs. Decreased TPR results in increased venous return as more blood is allowed to flow back to the heart from the arterial side.
    - An **upward shift of the cardiac output curve** is caused by the decreased aortic pressure (decreased afterload) as the heart pumps against a lower pressure.
    - As a result of these simultaneous changes, a new equilibrium point is established at which both **cardiac output** and **venous return** are **increased**, but right atrial pressure is unchanged.

DYNAMICS OF THE MICROCIRCULATION

Structure of Capillary Bed

- Metarterioles branch into the capillary beds. At the junction of the arterioles and capillaries is a smooth muscle band called the **precapillary sphincter**.
- True capillaries do not have smooth muscle; they consist of a single layer of **endothelial cells** surrounded by a basement membrane.
- **Clefts (pores)** between the endothelial cells allow passage of water-soluble substances. The clefts represent a very small fraction of the surface area (<0.1 %).
- Blood flow through the capillaries is regulated by contraction and relaxation of the arterioles and the precapillary sphincters.

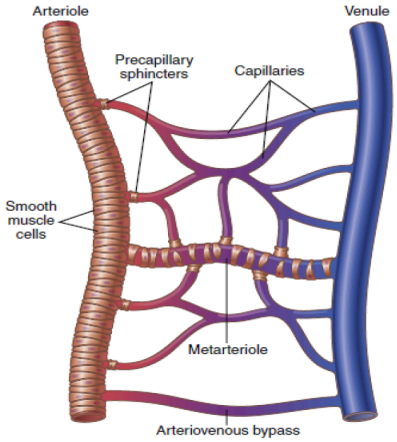

Figure 16-1. Components of the microcirculation.

Substances that can cross the capillary wall and the mechanisms involved in their passage across the capillary wall

- **Lipid-soluble substances**
  - Cross the membranes of the capillary endothelial cells by **simple diffusion.**
  - Include **O2** and **CO2**.
- **Small water-soluble substances**
  - Cross via the water-filled clefts between the endothelial cells.
  - Include **water, glucose,** and **amino acids**.
  - Generally, protein molecules are too large to pass freely through the clefts.
  - In the **brain**, the clefts between endothelial cells are exceptionally tight **(blood-brain barrier).**
  - In the **liver** and **intestine**, the clefts are exceptionally wide and allow passage of protein. These capillaries are called **sinusoids**.
- **Large water-soluble substances**
  - Can cross by **pinocytosis**.

Factors that influence transcapillary movement (Starling Hypothesis) and how they maintain normal fluid movement

- The Starling equation

$$J_v = K_f\left[(P_c - P_i) - (\pi_c - \pi_i)\right]$$

where:
J_v = fluid movement (mL/min)
K_f = hydraulic conductance (mL/min·mm Hg)
P_c = capillary hydrostatic pressure (mm Hg)
P_i = interstitial hydrostatic pressure (mm Hg)
π_c = capillary oncotic pressure (mm Hg)
π_i = interstitial oncotic pressure (mm Hg)

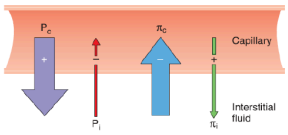

FIGURE 3.18 Starling forces across the capillary wall. + *sign* = favors filtration; − *sign* = opposes filtration; P_c = capillary hydrostatic pressure; P_i = interstitial hydrostatic pressure; π_c = capillary oncotic pressure; π_i = interstitial oncotic pressure.

- **Jv** is **fluid flow**.
  - When **Jv is positive**, there is net fluid movement out of the capillary **(filtration)**.
  - When **Jv is negative**, there is net fluid movement into the capillary **(absorption)**.
- **Kf** is the **filtration coefficient**.
  - It is the hydraulic conductance (**water permeability**) of the capillary wall.
- **Pc** is **capillary hydrostatic pressure**.

- An increase in Pc **favors filtration** out of the capillary.
- Pc is determined by arterial and venous pressures and resistances.
- An increase in either arterial or venous pressure produces an increase in Pc; increases in venous pressure have a greater effect on Pc.
- Pc is higher at the arteriolar end of the capillary than at the venous end (except in glomerular capillaries, where it is nearly constant).

- **Pi** is **interstitial fluid hydrostatic pressure**.
  - An increase in Pi **opposes filtration** out of the capillary.
  - It is normally close to 0 mm Hg (or it is slightly negative).
- π**c** is **capillary oncotic** or **colloid osmotic pressure**.
  - An increase in πc **opposes filtration** out of the capillary.
  - πc is increased by increases in the protein concentration in the blood (e.g., dehydration).
  - πc is decreased by decreases in the protein concentration in the blood (e.g., nephrotic syndrome, protein malnutrition, liver failure).
  - Small solutes do not contribute to πc.
- π**i** is **interstitial fluid oncotic pressure**.
  - An increase in πi **favors filtration** out of the capillary.
  - πi is dependent on the protein concentration of the interstitial fluid, which is normally quite low because very little protein is filtered.

Factors that increase filtration

- ↑**Pc**- caused by increased arterial pressure, increased venous pressure, arteriolar dilation, and venous constriction
- ↓**Pi**
- ↓ π**c-** caused by decreased protein concentration in the blood
- ↑ π**i**- caused by inadequate lymphatic function

FACTORS THAT CONTROL BLOOD FLOW AND THE MECHANISM INVOLVED

Local (Intrinsic) Control

- **Examples of local control**
  - **Autoregulation**
    - Blood flow to an organ remains constant over a wide range of perfusion pressures.
    - Organs that exhibit autoregulation are the heart, brain, and kidney.
    - For example, if perfusion pressure to the heart is suddenly decreased, compensatory vasodilation of the arterioles will occur to maintain a constant flow
  - **Active hyperemia**
    - Blood flow to an organ is proportional to its metabolic activity.
    - For example, if metabolic activity in skeletal muscle increases as a result of strenuous exercise, blood flow to the muscle will increase proportionately to meet metabolic demands.
  - **Reactive hyperemia**
    - Is an increase in blood flow to an organ that occurs after a period of occlusion of flow.
    - The longer the period of occlusion is, the greater the increase in blood flow is above pre-occlusion levels.
- **Mechanisms that explain local control of blood flow**
  - **Myogenic hypothesis**
    - Explains autoregulation, but not active or reactive hyperemia
    - Is based on the observation that vascular smooth muscle contracts when it is stretched.
    - For example, if perfusion pressure to an organ suddenly increases, the arteriolar smooth muscle will be stretched and will contract. The resulting vasoconstriction will maintain a constant flow (without vasoconstriction, blood flow would increase as a result of the increased pressure).
  - **Metabolic hypothesis**
    - Is based on the observation that the tissue supply of O2 is matched to the tissue demand for O2.
    - Vasodilator metabolites are produced as a result of metabolic activity in tissue. These vasodilators are CO2, H+, K+, lactate, and adenosine.
    - Examples of active hyperemia:
      - √ If the metabolic activity of a tissue increases (e.g., strenuous exercise), both the demand for O2 and the production of vasodilator metabolites increase. These metabolites cause arteriolar vasodilation, increased blood flow, and increased O2 delivery to the tissue to meet demand.
      - √ If blood flow to an organ suddenly increases as a result of a spontaneous increase in arterial pressure, then more O2 is provided for metabolic activity. At the same time, the increased flow "washes out" vasodilator metabolites. As a result of this "washout," arteriolar vasoconstriction occurs, resistance increases, and blood flow is decreased to normal.

Humoral (Extrinsic) Control of blood flow

- **Sympathetic innervation of vascular smooth muscle**
  - Increases in sympathetic tone cause vasoconstriction.
  - Decreases in sympathetic tone cause vasodilation.
  - The density of sympathetic innervation varies widely among tissues. Skin has the greatest innervation, whereas coronary, pulmonary, and cerebral vessels have little innervation.
- **Other vasoactive hormones**
  - **Histamine**
    - Causes arteriolar dilation and venous constriction.
    - The combined effects of arteriolar dilation and venous constriction cause increased Pc and increased filtration out of the capillaries, resulting in local edema.
    - Is released in response to tissue trauma.
  - **Bradykinin**
    - Causes arteriolar dilation and venous constriction.
    - Produces increased filtration out of the capillaries (similar to histamine) and causes local edema.
  - Serotonin (5-hydroxytryptamine)
    - Causes **arteriolar constriction** and is released in response to blood vessel damage to help prevent blood loss.
    - Has been implicated in the vascular spasms of **migraine headaches**
  - Prostaglandins
    - **Prostacyclin** is a vasodilator in several vascular beds.
    - **E-series prostaglandins** are vasodilators.
    - **F-series prostaglandins** are vasoconstrictors.
    - **Thromboxane A2** is a vasoconstrictor.

Coronary circulation

- Is controlled almost entirely by **local metabolic factors**.
- Exhibits autoregulation.
- Exhibits active and reactive hyperemia.
- The most important local metabolic factors: **hypoxia** and **adenosine**.

- For example, increases in myocardial contractility are accompanied by an increased demand for O2. To meet this demand, compensatory vasodilation of coronary vessels occurs and, accordingly, both blood flow and O2 delivery to the contracting heart muscle increase (active hyperemia).
- During **systole**, mechanical compression of the coronary vessels reduces blood flow. After the period of occlusion, blood flow increases to repay the O2 debt (reactive hyperemia).
- Sympathetic nerves play a minor role.

LYMPHATICS

Functions

- The lymphatic system represents an accessory route through which fluid can flow from the interstitial spaces into the blood.
- Most importantly, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function, without which we would die within about 24 hours.

Functional Anatomy

Types of lymphatic vessels

- Initial lymphatics – lack valves and smooth muscle in their walls
  - They are found in regions such as the intestine or skeletal muscle.
  - Tissue fluid enters them through loose junctions between the endothelial cells that form their walls.
  - The fluid in them apparently is massaged by muscle contractions of the organs and contraction of arterioles and venules, with which they are often associated.
  - They drain into the collecting lymphatics
- Collecting lymphatics – have valves and smooth muscle in their walls and contract in a peristaltic manner, propelling the lymph along the vessels.
  - Flow in the collecting lymphatics is further aided by movements of skeletal muscle, the negative intrathoracic pressure during inspiration, and the suction effect of high velocity flow of blood in the veins in which the lymphatics terminate. However, the contractions are the principal factor propelling the lymph.

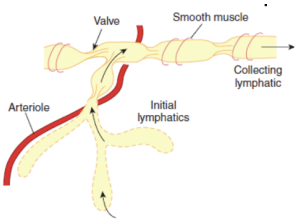

FIGURE 31–32 Schematic of the lymphatic system. Initial lymphatics are highly permeable structures without smooth muscle or valves. Unidirectional flow is accomplished in the collecting lymphatics, which appear like a string of beads due to the regular valves. Lymphatics are often close to blood vessels, whose contractions also encourage flow in the lymphatic system.

Lymph channels in the body

- Almost all tissues of the body have special lymph channels that drain excess fluid directly from the interstitial spaces. The exceptions include the superficial portions of the skin, central nervous system, endomysium of muscles, and bones.
  - However, even these tissues have minute interstitial channels called **prelymphatics** through which interstitial fluid can flow; this fluid eventually empties into lymphatic vessels or, in the case of the brain, into the cerebrospinal fluid and then directly back into the blood.
- Essentially all the lymph vessels from the lower part of the body eventually empty into the **thoracic duct**, which in turn empties into the blood venous system at the juncture of the **left internal jugular vein** and **left subclavian vein**.

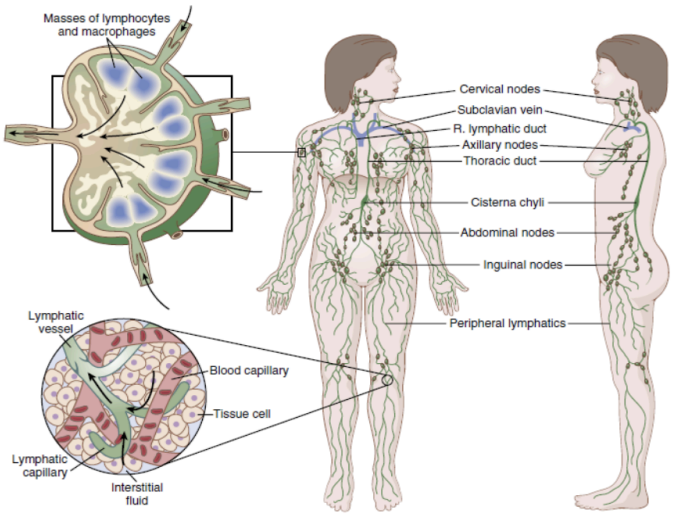

Figure 16-6. The lymphatic system.

- Lymph from the **left side of the head**, **left arm**, and **parts of the chest region** also enters the thoracic duct before it empties into the veins.
- Lymph from the **right side of the neck and head**, **right arm**, and **parts of the right thorax** enters the right lymph duct (much smaller than the thoracic duct), which empties into the blood venous system at the juncture of the right subclavian vein and internal jugular vein.
- **Terminal Lymphatic Capillaries and Their Permeability.**
  - Most of the fluid filtering from the **arterial ends** of blood capillaries flows among the cells and finally is reabsorbed back into the **venous ends** of the blood capillaries but, on average, about 1/10th of the fluid instead enters the **lymphatic capillaries** and returns to the blood through the lymphatic system rather than through the venous capillaries.
- The total quantity of all this lymph is normally only **2 to 3 L/day**.
- The fluid that returns to the circulation by way of the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way, although they can enter the lymphatic capillaries almost unimpeded. The reason for this mechanism is a special structure of the lymphatic capillaries, demonstrated in Figure 16-7.
  - This figure shows the endothelial cells of the lymphatic capillary attached by **anchoring filaments** to the surrounding connective tissue.
  - At the junctions of adjacent endothelial cells, the edge of one endothelial cell overlaps the edge of the adjacent cell in such a way that the overlapping edge is free to flap inward, thus forming a minute valve that opens to the interior of the lymphatic capillary.
  - Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary. However, this fluid has difficulty leaving the capillary once it has entered because any backflow closes the flap valve. Thus, the lymphatics have valves at the very tips of the terminal lymphatic capillaries, as well as valves along their larger vessels, up to the point where they empty into the blood circulation.

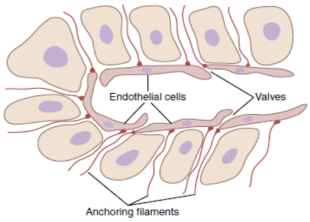

Figure 16-7. Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

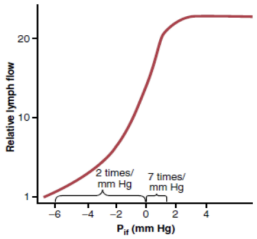

Figure 16-8. Relationship between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure (P_{if}) rises slightly above atmospheric pressure (0 mm Hg). (*Courtesy Dr. Harry Gibson and Dr. Aubrey Taylor.*)

Formation of Lymph

- Lymph is derived from interstitial fluid that flows into the lymphatics. Therefore, lymph as it first enters the terminal lymphatics has almost the same composition as the interstitial fluid.
- The protein concentration in the interstitial fluid of most tissues averages about **2 g/dL**, and the protein concentration of lymph flowing from these tissues is near this value.
- Lymph formed in the liver has a protein concentration as high as **6 g/dL**, and lymph formed in the intestines has a protein concentration as high as **3 to 4 g/dL**.
    - Because about two thirds of all lymph normally is derived from the liver and intestines, the thoracic duct lymph, which is a mixture of lymph from all areas of the body, usually has a protein concentration of **3 to 5 g/dL**.
- The lymphatic system is also one of the major routes for absorption of nutrients from the gastrointestinal tract, especially for absorption of virtually all fats in food.
    - After a fatty meal, thoracic duct lymph sometimes contains as much as 1% to 2% fat.
- Finally, even large particles, such as bacteria, can push their way between the endothelial cells of the lymphatic capillaries and in this way enter the lymph. As the lymph passes through the lymph nodes, these particles are almost entirely removed and destroyed.

Rate of Lymph Flow

- About **100 mL/hr** of lymph flows through the thoracic duct of a resting human, and approximately another **20 mL** flows into the circulation each hour through other channels, making a total estimated lymph flow of about **120 mL/hr** or **2 to 3 L/day**.
- **Factors that determine the rate of lymph flow**
    - **Interstitial fluid pressure**
      Figure 16-8 shows the effect of different levels of interstitial fluid hydrostatic pressure on lymph flow, as measured in animals.
    - Note that normal lymph flow is very little at interstitial fluid pressures more negative than the normal value of **-6 mm Hg**. Then, as the pressure rises to **0 mm Hg** (**atmospheric pressure**), flow increases more than 20-fold.
    - Therefore, any factor that increases interstitial fluid pressure also increases lymph flow if the lymph vessels are functioning normally. Such factors include the following:
        - Elevated capillary hydrostatic pressure
        - Decreased plasma colloid osmotic pressure
        - Increased interstitial fluid colloid osmotic pressure
        - Increased permeability of the capillaries
    - All these factors favor net fluid movement into the interstitium, thus increasing interstitial fluid volume, interstitial fluid pressure, and lymph flow all at the same time.
    - However, note in Figure 16-8 that when the interstitial fluid hydrostatic pressure becomes 1 or 2 mm Hg greater than atmospheric pressure (>0 mm Hg), lymph flow fails to rise any further at still higher pressures. This results from the fact that the increasing tissue pressure not only increases entry of fluid into the lymphatic capillaries, but also compresses the outside surfaces of the larger lymphatics, thus impeding lymph flow.
    - At the higher pressures, these two factors balance each other, so lymph flow reaches a maximum flow rate. This maximum flow rate is illustrated by the upper level plateau in Figure 16-8.
- **Lymphatic pump-** increases lymph flow
    - Valves exist in all lymph channels. Figure 16-9 shows typical valves for collecting lymphatics into which the lymphatic capillaries empty.
    - Videos of exposed lymph vessels in animals and in humans have shown that when a collecting lymphatic or larger lymph vessel becomes **stretched with fluid**, the smooth muscle in the wall of the vessel automatically contracts.
        - Furthermore, each segment of the lymph vessel between successive valves functions as a separate automatic pump. That is, even slight filling of a segment causes it to contract, and the fluid is pumped through the next valve into the next lymphatic segment.
        - This fluid fills the subsequent segment and a few seconds later it also contracts, with the process continuing all along the lymph vessel until the fluid is finally emptied into the blood circulation.
- In a very large lymph vessel, such as the thoracic duct, this lymphatic pump can generate pressure as high as **50 to 100 mm Hg**.
- **Pumping Caused by External Intermittent Compression of the Lymphatics**
    - In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel can also cause pumping. In order of their importance, such factors are as follows:
        - Contraction of surrounding skeletal muscles
        - Movement of the parts of the body
        - Pulsations of arteries adjacent to the lymphatics
        - Compression of the tissues by objects outside the body
    - The lymphatic pump becomes very active during exercise, often increasing lymph flow 10-to 30-fold. Conversely, during periods of rest, lymph flow is sluggish (almost zero).

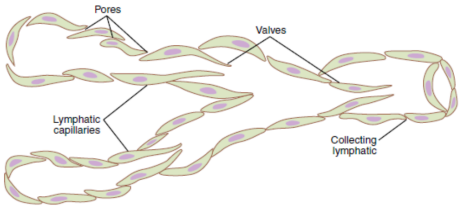

Figure 16-9. Structure of lymphatic capillaries and a collecting lymphatic, with the lymphatic valves also shown.

- **Lymphatic capillary pump**
    - The terminal lymphatic capillary is also capable of pumping lymph, in addition to the pumping by the larger lymph vessels.
    - The **anchoring filaments** on the walls of the lymphatic capillaries tightly adhere to the surrounding tissue cells.
        - Therefore,each time excess fluid enters the tissue and causes the tissue to swell, the anchoring filaments pull on the wall of the lymphatic capillary, and fluid flows into the terminal lymphatic capillary through the junctions between the endothelial cells.
        - Then, when the tissue is compressed, the pressure inside the capillary increases and causes the overlapping edges of the endothelial cells to close like valves. Therefore, the pressure pushes the lymph forward into the collecting lymphatic instead of backward through the cell junctions.

- The lymphatic capillary endothelial cells also contain a few contractile **actomyosin filaments**.
  - In some animal tissues (e.g., a bat wing), these filaments have been observed to cause rhythmical contraction of the lymphatic capillaries in the same rhythmic way that many of the small blood vessels and larger lymphatic vessels contract.
  - Therefore,it is probable that at least part of lymph pumping results from lymph capillary endothelial cell contraction in addition to contraction of the larger muscular lymphatics.

Summary of Factors that Determine Lymph Flow

- From the previous discussion, one can see that the two primary factors that determine lymph flow are (1) the **interstitial fluid pressure** and (2) the **activity of the lymphatic pump**.
- Therefore, one can state that, roughly, the rate of lymph flow is determined by the product of interstitial fluid pressure times the activity of the lymphatic pump.

Other Important Roles of the Lymphatic System

- **Lymphatic System Plays a Key Role in Controlling Interstitial Fluid Protein Concentration, Volume, and Pressure**
  - It is already clear that the lymphatic system functions as an overflow mechanism to return excess proteins and excess fluid volume from the tissue spaces to the circulation.
  - Therefore, the lymphatic system also plays a central role in controlling the following: (1) **concentration of proteins in the interstitial fluids**; (2) **volume of interstitial fluid**; and (3) **interstitial fluid pressure**. Here is an explanation of how these factors interact.

1. Remember that **small amounts of proteins leak continuously** out of the **blood capillaries** into the interstitium.
   a. Only minute amounts, if any, of the leaked proteins return to the circulation by way of the venous ends of the blood capillaries.
   b. Therefore, these proteins tend to accumulate in the interstitial fluid, which in turn increases the colloid osmotic pressure of the interstitial fluids.
2. The **increasing colloid osmotic pressure** in the interstitial fluid shifts the balance of forces at the blood capillary membranes in favor of fluid filtration into the interstitium.
   a. Therefore, in effect, fluid is translocated osmotically outward through the capillary wall by the proteins and into the interstitium, thus increasing both interstitial fluid volume and interstitial fluid pressure.
3. The **increasing interstitial fluid pressure** greatly increases the rate of lymph flow, which carries away the excess interstitial fluid volume and excess protein that has accumulated in the spaces.

- Thus, once the interstitial fluid protein concentration reaches a certain level and causes comparable increases in interstitial fluid volume and pressure, the return of protein and fluid by way of the lymphatic system becomes great enough to balance the rate of leakage of these into the interstitium from the blood capillaries.
  - Therefore, the quantitative values of all these factors reach a steady state, and they remain balanced at these steady state levels until some factor changes the rate of leakage of proteins and fluid from the blood capillaries.
- **Significance of Negative Interstitial Fluid Pressure for Holding Body Tissues Together**
  - Traditionally, it has been assumed that the different tissues of the body are held together entirely by **connective tissue fibers**.
  - However, connective tissue fibers are very weak or even absent at many places in the body, particularly at points where tissues slide over one another (e.g., skin sliding over the back of the hand or over the face). Yet, even at these places, the tissues are held together by the **negative interstitial fluid pressure**, which is actually a partial vacuum.
  - When the tissues lose their negative pressure, fluid accumulates in the spaces, and the condition known as **edema** occurs.