Terms you should understand: hemorrhage, intrinsic and extrinsic mechanisms, anoxia, myocardial contractility, residual volume of ventricles, venous return to the heart, adrenal medulla, baroreceptors, stretch receptors, aortic arch, carotid sinuses, systolic pressure, diastolic pressure, pulse pressure, average blood pressure, atherosclerosis, local factors, paracines, angiotensin, vasoconstriction, vasodilation, angiotensin, hypovolemic shock, anaphylactic shock.

I. Cardiovascular regulation goes on all the time, even when there aren’t any major physiological crises.

A. One major challenge in cardiovascular regulation is that the potential volume of the circulatory system is vastly greater than the normal volume of blood.

1. An important function of regulation is to match the capacity of the vascular system to the volume of the blood.
   a. For example, if significant blood volume is lost (hemorrhage), blood pressure will drop unless vascular resistance increases and/or the heart contracts more strongly.
   b. Blood pressure and blood flow is modulated continuously to supply blood to the brain and to the heart—and to the rest of the tissues as long as it’s possible.

2. Regulation of the blood vessels takes place by control contractions of unitary smooth muscles in the walls of blood vessels by ACh, NorEpi, and Epi.

B. A second major challenge in cardiovascular regulation is that we stand upright.

1. In our upright posture, gravity pulls blood away from our head toward our feet—but the brain requires sufficient oxygen or it stops functioning.

2. If the blood pressure is not sufficient to force blood to the head, the brain becomes ischemic and we faint, a very effective (and dramatic) negative feedback mechanism.

II. Heart and blood vessels regulate blood flow to all tissues, by both intrinsic (Starling Law) and extrinsic (neurons and hormones) mechanisms.

A. Cardiac output (CO) = heart rate X stroke volume

1. In a 120 pound resting adult, CO is about 5 liters per minute (70 beats/minute X 70 ml/beat).

2. A well-trained athlete, exercising maximally, CO can be as high as 35 liters per minutes.

B. Control of heart rate.

1. Increased sympathetic activity (including activity of the adrenal medulla) increases blood flow to tissues (e.g., skeletal muscles) that support strenuous physical activity.
   a. It reduces the supply of blood to organs such as the intestines.
   b. It generally increases average blood pressure.

2. Increased parasympathetic activity increases blood flow to tissues that support housekeeping functions, such as digestion.
   a. It reduces the supply of blood to skeletal muscles is decreased.

Fig. 14.1. Feedback diagram summarizing the relationship between cardiac output and arterial blood pressure.
b. It generally decreases average blood flow.

Fig. 14.2. Feedback diagram adding the influences of the sympathetic and parasympathetic nervous systems on the control of arterial blood pressure.

Experiment: Measure changes in heart rate while stimulating both the vagus nerve (Vag) at different frequencies (shown is 8 Hz, 4 Hz, and no stimulation (0 Hz)) and the sympathetic nerves at 1, 2, and 4 Hz.

Conclusions:
(1) Increasing sympathetic stimulation increases the heart rate.
(2) Parasympathetic activity has a stronger effect on heart rate than does sympathetic activity.

Fig. 14.3. How stimulating parasympathetic and sympathetic nerves simultaneously affects heart rate.

3. Drugs can block autonomic neurotransmitter receptors to change the heart rate.
   a. Atropine (a muscarinic ACh blocker) increases heart rate
   b. Propranolol (a ß-adrenergic blocker) slows heart rate.
D. Reflex arcs regulate the extrinsic control of blood pressure.

1. The major sensors are stretch receptors that lie in two locations:
   a. **aortic arch**, just outside the left ventricle.
   b. **carotid arteries**, which are the major arteries that carry blood to the brain.

![Fig. 14.5. Locations of the aortic and carotid sinus baroreceptors.](image)

2. Respond to stretch of arterial walls, but are called **baroreceptors** because they are activated by increases in blood pressure.

![Fig. 14.4. How blocking parasympathetic and sympathetic activity with drugs affects heart rate. Ten 21 year-old men were treated with Atropine and Propranolol for 4 days. Half were treated with Atropine for the first 4 days, the other 5 were treated with Propranolol for the first 5 days.](image)
3. Baroreceptor activity activates neurons in nuclei in the medulla and in the hypothalamus.

4. The outputs are the autonomic pathways that control the heart and blood vessels.
   a. Increased activity in these baroreceptors activates a reflex arc that decreases heart rate.
      i. For moderate increases in blood pressure, parasympathetic activity (in the vagus nerve) increases and sympathetic activity (in sympathetic nerves) decreases.
      ii. For increases of more than 30 mm Hg, sympathetic activity is totally silenced.
   b. A decrease in pressure detected by these baroreceptors leads to an increase in the heart rate and in the contractility of the ventricles; sympathetic activity increases and parasympathetic activity decreases.
      i. A small drop in blood pressure completely silences parasympathetic activity.
ii. This asymmetry in the sympathetic and parasympathetic responses indicates that increasing cardiac output is more important than decreasing it.

Fig. 14.8. Reflex responses of the parasympathetic (upper graph) and sympathetic (lower graph) nerve activity to changes in blood pressure at the aortic sinus.
c. Baroreceptor activity also activate reflexes that change the state of the blood vessels.

Fig. 14.9. Feedback diagram adding the influences of the baroreceptors and local tissue factors on the control of arterial blood pressure.

III. Several different features are modified in the regulation of cardiovascular function:

A. Behavior of cardiac muscle fibers
   1. Heart rate.
   2. Myocardial contractility.

B. Factors that depend on both the heart and the blood vessels
   1. Ventricular filling: depends on venous return and the pressure driving it.
   2. Ventricular residual volume: depends on stroke volume, which depends on contractility.
   3. Normally, venous return to the heart is the factor that limits cardiac output.
      a. With no parasympathetic innervation, heart can pump 10-13 liters of blood a minute; normal venous return is about 5 liters per minute.
      b. Venous return is affected by:
         i. Total peripheral resistance.
         ii. Level of muscular exertion (the "muscle pump").
         iii. Posture (e.g., a standing person has more hydrostatic pressure modifying the pressure of heart contractions)
         iv. Respiratory movements of the diaphragm generate negative pressure on great veins.

C. Activity in the autonomic nervous system
1. Normally, sympathetic and parasympathetic systems are both active simultaneously and tonically.
   a. The parasympathetic system slows the heart; it primarily affects heart rate.
      i. Slower rate gives longer filling time, so each pulse of blood can be larger; ventricular filling is increased.
      ii. The Starling Law assures that each stroke volume is larger than normal.
      iii. Usually the slower heart rate produces a lower cardiac output because the increased filling time does not compensate for the decreased rate.
   b. Sympathetic innervation both speeds up the heart and increases myocardial contractility.
      i. When heart rate increases, the time available for filling and for contraction decreases, which could cause a net decrease in cardiac output if there were not compensation.
      ii. The ventricles also increase their strength of contraction in order for each contraction to expel the same amount of blood at the faster rate that each contraction does at a slower rate.
      iii. Overall effect of sympathetic drive is to speed up the heart and to strengthen the contractions, which decreases the ventricular residual volume.
   c. Sympathetic nervous system affects the tone in the arterioles.
      i. Increased average state of vasoconstriction leads to an increase in mean blood pressure.
      ii. Increased blood pressure changes the load against which the left heart pumps, particularly the fraction of each contraction during which blood can be ejected.
   d. In addition, the heart rate is coupled to breathing motions via the autonomic nervous system.

D. The adrenal medulla also acts on the heart and blood vessels.
   1. The adrenal medulla is activated by the sympathetic nervous system.
   2. It secretes epinephrine (mostly) and norepinephrine (a little) into the circulation.

IV. Cardiovascular regulation; the grand scheme (Fig. 14.10)

A. Four components of blood pressure that can vary independently:
   1. **Diastolic pressure**: lowest pressure at any time in the circulation.
      a. Depends on the total resistance in the systemic loop
      b. Determines how readily blood can flow away from the aorta and into the systemic vasculature.
   2. **Pulse pressure**: amount of pressure increase produced by each ventricular contraction; determines stroke volume.
   3. **Systolic pressure**: the sum of pulse pressure and diastolic pressure.
   4. **Average blood pressure** is the integrated average of systolic and diastolic pressures.
      • it approximates how successfully blood is delivered to the peripheral tissues, especially those higher than the heart.

B. Two classes of mechanisms affect systemic blood pressure. (Pulmonary circulation pressure varies much less than the systemic blood pressure does, but the controlling variables are similar.)
   1. **Cardiac factors**: stroke volume and heart rate affect cardiac output.
   2. **Peripheral factors**: peripheral resistance of the vasculature.
      a. Peripheral resistance depends on the diameter of the arteries and arterioles. Remember, the arterioles are called the main resistance elements.
i. Sympathetic nervous activity reduces the diameter of blood vessels by activating the smooth muscles in the body wall.

ii. Constriction of arterioles is the most important factor regulating blood pressure, but blood can be shifted out of the veins and back to the heart by venuconstriction. Sympathetic activity causes venuconstriction, but is a less common event than arterial constriction.

iii. Pathological conditions like atherosclerosis can increase the average blood pressure by narrowing the lumen of arteries and increasing the rigidity of their walls.

b. Total peripheral resistance decreases when more capillary beds open in parallel.

**Cardiovascular regulation**

![Feedback diagram showing all the influences on the control of arterial blood pressure.](image_url)

**Fig. 14.10.** Feedback diagram showing all the influences on the control of arterial blood pressure.

C. Peripheral resistance is modulated by nervous, hormonal, and local mechanisms.

1. Blood flows into vascular beds with the least resistance, so the state of vasodilation or vasoconstriction in arterioles determines where blood will flow.

2. Activity of sympathetic neurons changes the contraction of smooth muscles in the walls of blood vessels.

   a. Most vascular smooth muscles contract in response to norepinephrine (also to epinephrine, but with lower sensitivity), by binding to α-adrenergic receptors.

   b. However, vascular smooth muscles in some arterioles (e.g., skeletal muscle and smooth muscles in the arterioles of the coronary circulation) relax in response to Epi and NorEpi.

   c. Within working skeletal muscles, the arterioles dilate, largely due to the release of local factors (e.g., products of metabolism, paracrices).
d. The overall effect of an increase in catecholamines is an increase in total peripheral resistance.
3. Hormones modify peripheral resistance by acting on vascular smooth muscles.
   a. **Epi** (and a little **Nor Epi**) from the adrenal medulla in response to sympathetic activity.
   b. **Vasopressin (ADH)** is secreted by neurons, via the neurohypophysis, in response to--among other things--a drop in blood pressure or an increase in blood osmolarity.
   c. **Angiotensin** is generated via a renal (kidney) reflex loop in responses to changes in the amount of blood that perfuses the kidney.

4. Relaxation of pre-capillary sphincters driven by local metabolic factors also can play a major role in varying peripheral resistance in some tissues, but not all tissues.

5. Exercise provides an excellent example of the regulation of blood flow: cardiac output increases as the intensity of exercise increases.

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**Fig. 14.11.** Blood flow to different parts of the body at rest (left end of the graph). The proportions change as we exercise, as measured by oxygen uptake, up to maximal intensity of exercise (right end of the graph).

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a. Total cardiac output increases about 4-fold as exercise reaches maximal intensity.

b. Blood flow to the viscera diminishes as blood flow to the muscles increases nearly 20-fold.

D. Kidney function is another peripheral factor that profoundly affects blood pressure by modulating the total fluid volume in the body. (We will talk about this in the next section of the course.)

VI. In shock, venous return to the heart drops, which causes cardiac output to drop, which causes venous return to the heart to drop......a positive feedback loop.

A. In **hypovolemic (or hemorragic) shock**, the loss of a significant volume of blood is the initial cause of the drop in venous return to the heart. Loss of blood causes a mismatch between the volume of blood and the available volume of the vascular system.

B. In **anaphylactic shock**, a massive allergic reaction causes a large amount of histamine to be liberated, and histamine is a powerful vasodilator. As a result, many arterioles dilate, especially in the abdominal cavity, and there is a serious mismatch between the volume of open blood vessels and the volume of blood. As a result venous return to the heart drops, etc.