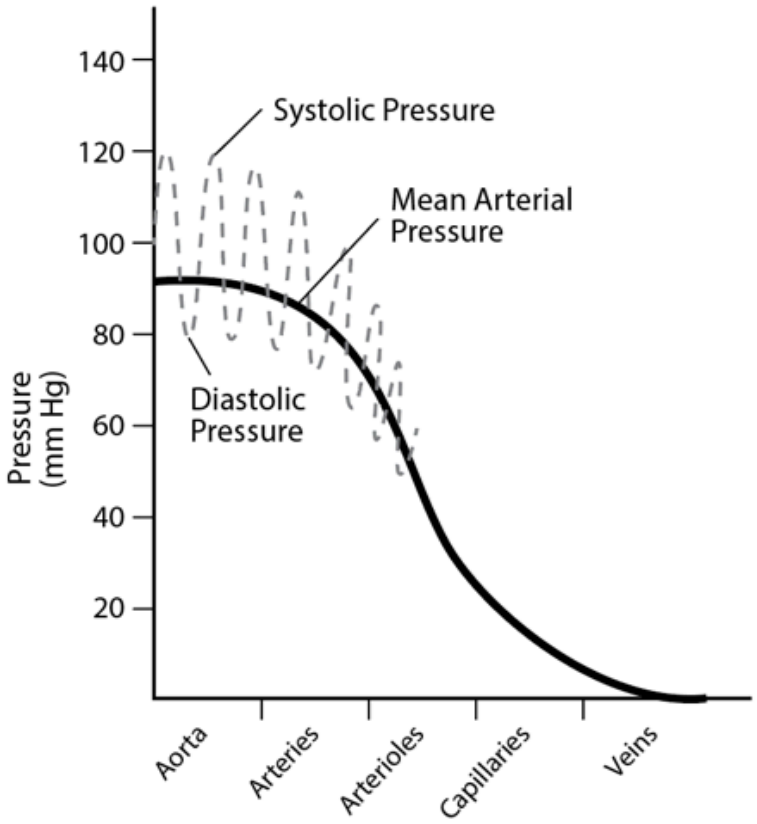
3.5.3

Blood Pressure Regulation and Shock

Blood pressure is tightly controlled. Homeostatic mechanisms assure that blood pressure does not get too low or life sustaining organs like the brain can be in danger of permanent damage. You may hear the term **Pulse Pressure**. Pulse pressure is the pressure difference between the peak systolic and diastolic pressures. For example, if the systolic pressure is 120 mmHg and the diastolic pressure is 80 mmHg, then the pulse pressure is 40 mmHg.

Another term to understand is **Mean Arterial Pressure (MAP). MAP is equal to the cardiac output multiplied by the total peripheral resistance (PR).** Another way in which MAP can be calculated is by taking a weighted average of systolic and diastolic blood pressure. Weighted average means that diastolic pressure has more influence on the "average" pressure for arteries because diastole lasts longer than systole. MAP is calculated using the formula: **MAP=Diastolic Pressure + 1/3 (Systolic Pressure - Diastolic Pressure).**

The image below shows the mean arterial pressure as a solid line dropping from about 100 in the aorta to 0 in the veins.



Mean Arterial Pressure Difference throughout the Blood Vessels.

Image drawn by J. Shaw at BYU-Idaho Fall 2013

$$MAP = CO \times PR$$

$$CO = HR \times SV$$

$$PR \propto L*V/r^4$$

MAP = Mean Arterial Pressure; CO = Cardiac Output; PR=Peripheral Resistance;

HR= Heart Rate; SV=Stroke Volume; L = Length; V=Viscosity; r=radius of a blood vessel

The concept of "$PR \propto L*V/r^4$" Comes from work done by a French physicist named Jean Léonard Marie Poiseuille (1797 - 1869). Poiseuille studied flowrates of fluid in pipes. His principles apply relatively well to human blood vessels.

Two equations help define his work on flowrate.

$$Flow\ Rate = \frac{(P^1 - P^2)}{PR}$$

This equation suggests that more fluid will flow through a vessel if the pressure difference from the start (P1) and end (P2) of the vessel is high (i.e. a high blood pressure) and the peripheral resistance to blood flow (PR) is low. This second equation defines the factors that determine peripheral resistance.

$$PR = \frac{8VL}{\pi r^4}$$

When these two equations are combined we get an equation that defines "Poiseuille's Law".

$$Flow\ Rate = \frac{\pi\ (\Delta\ Pressure)(r^4)}{8VL}$$

According to Poiseuille's Law, vasodilation would result in a very significant increase in blood flow through a vessel. Also, vasoconstriction would cause blood flow to drop (notice "r" to the 4th power). The muscular arteries and arterioles of the human circulatory system can change their radius remarkably with vasodilation and vasoconstriction.

The blood pressure in the large arteries is what is being determined when a blood pressure is taken. The equations above help us visualize the variables that can regulate and change blood pressure. Notice that the peripheral resistance is listed as being "proportional" (use of the proportional symbol '$\propto$') to blood vessel length and blood viscosity but inversely proportional to radius of the blood vessel raised to the 4^{th} power! The proportional sign ($\propto$) is used because the actual equation for peripheral resistance uses some constants not shown here. We do not intend to actually calculate peripheral resistances, but we do want to see how the variables relate to each other.

Consider the following example:

During exercise, skeletal muscles contract, pumping and returning more blood to the heart. The heart beats with stronger contractions to evacuate the extra blood returning to the heart (increased venous return). This makes stroke volume go up. During exercise, heart rate also increases. If HR and SV increase, then CO increases and the equations above show us that an increase in CO would increase MAP. An increase in MAP helps maintain adequate blood flow to working muscles during exercise. A discussion of blood pressure is really a discussion of how the body controls the variables in the equations mentioned to keep blood pressure in homeostatic ranges.

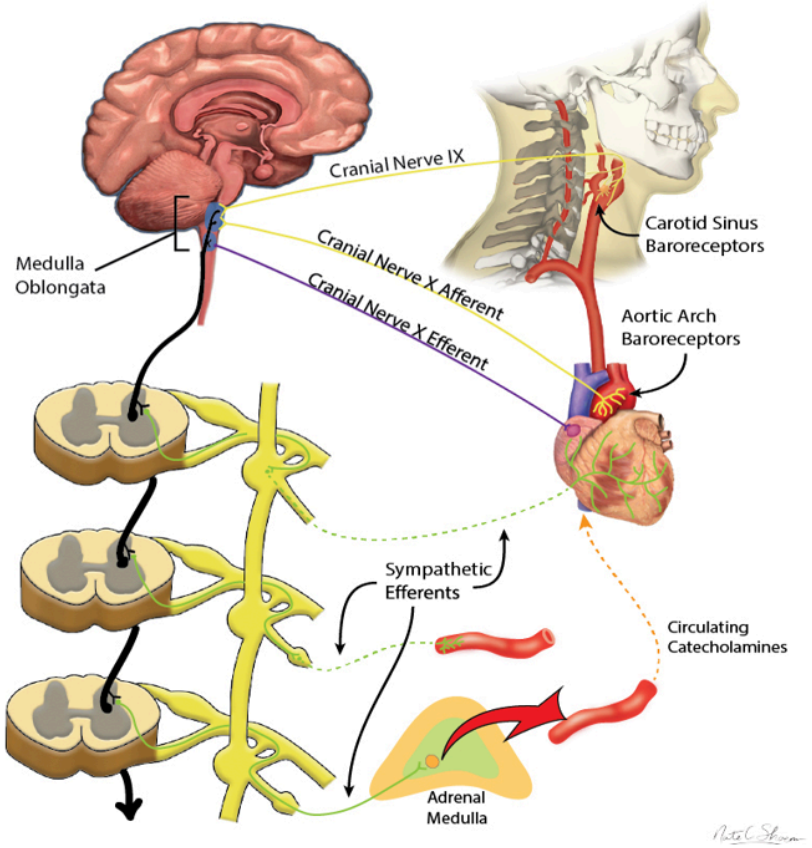
Short-Term Regulation

Short-term blood pressure regulation includes four responses: the baroreceptor reflex, the chemoreceptor reflex, the adrenal medullary mechanism and the central nervous system ischemic response.

Video on Baroreceptor Reflex

Baroreceptor Reflex

The ultimate role of the heart is to create sufficient pressure to ensure that blood flow to the body's tissues is maintained. Some tissues, like the cells of the brain and the cardiac muscle cells themselves, cannot survive for very long without a constant supply of blood. For example, brain cells die after only 4 or 5 minutes without oxygen. The baroreceptor reflex plays a key role in the short-term regulation of blood pressure. Like all reflexes, there are five components to this mechanism. We will describe the components and then explain what happens when there is a sudden change in blood pressure.



Baroreceptor reflex

Image modified by Nate Shoemaker (Spring 2016) using the following Wikimedia images: Title: Brain Anatomy (Sagittal) Author: BruceBlaus Site URL: https://commons.wikimedia.org/wiki/File:Brain _Anatomy_(Sagittal).png License: Public domain Title: Cervical vertebrae lateral2 Author: Was a bee Site URL: https://commons.wikimedia.org/wiki/File:Cervical _vertebrae_lateral2.png License: Public domain Title: Cervical vertebrae lateral2 Author: Was a bee Site URL: https://commons.wikimedia.org/wiki/File:Cervical _vertebrae_lateral2.png License: Public domain

1. **The receptors:** For this reflex the receptors are **baroreceptors** (pressure receptors) that reside in the arch of the aorta and in the carotid sinuses. The carotid sinuses are located in the internal carotid arteries immediately distal to the bifurcation of the common carotid arteries. These receptors are stretch receptors whose rate for generating action potentials is proportional to blood pressure, increased blood pressure results in increased stretch and an increase frequency of action potentials. Conversely, a drop in blood pressure deceases the frequency of action potentials generated by the receptors.

2. **Afferent pathway:** Action potentials from the carotid sinus receptors are transmitted to the brains stem via cranial nerve IX (glossopharyngeal) while action potentials from the aortic arch receptors are transmitted via cranial nerve X (Vagus)
3. **Integrating center:** Located in the medulla of the brain stem are the **cardiovascular centers** that regulate the rate and strength of contraction of the heart, as well as the diameter of the systemic blood vessels (primarily the arterioles).

4. **Efferent pathway:** Parasympathetic fibers extend from the cardiovascular centers of the medulla to the heart via the Vagus nerve. Sympathetic fibers travel through the cardiac sympathetic nerves to the heart. In addition, sympathetic fibers also project to the adrenal medulla where they stimulate the release of epinephrine and norepinephrine into the blood.
5. **Effector organ:** The effector organ in this reflex is the heart which can respond by increasing or decreasing cardiac output through changes in heart rate and strength of contraction. It should be pointed out that another effector organ in this reflex are the systemic arterioles. Their role in regulating blood pressure will be explained in the unit on blood vessels.

Now we will describe what happens when there is a sudden change in blood pressure. All of you have probably had the experience of quickly standing up and suddenly feeling light headed. This feeling is due to a transient decrease in blood flow to the brain. Fortunately, this happens only occasionally in most people. The reason you normally don't get light headed when you stand is due to the baroreceptor reflex. When we stand, blood flow to the brain decreases, due to gravity. Venous return decreases, cardiac output decreases, and blood pressure decreases. This is immediately sensed by the baroreceptors as they are stretched less. The reduced stretch results in a lower frequency of action potentials being transmitted to the cardiovascular centers, which is interpreted as a drop in blood pressure. The cardiovascular centers respond by decreasing parasympathetic activity and increasing sympathetic activity. These changes result in an increased rate of contraction as well as an increase in the strength of contraction, which increases cardiac output and restores blood flow to the brain. The reflex can respond within about two heartbeats of the time of the change. Take a moment and try a little experiment. While sitting quietly find the carotid pulse in your neck with your index finger. After you have an idea of how fast your heart is beating quickly stand and see if you can detect a change. What happened when you stood up? One more assignment: see if you can explain the series of events that would take place if there were a sudden increase in blood pressure.

Chemoreceptor Reflex

We have just described what happens when blood flow to the brain changes. However, there may be situations when blood flow doesn't change but the amount of oxygen delivered to the tissues decreases. This would happen if the oxygen content of the blood were to change and carbon dioxide levels increase, such as when there is respiratory distress due to illness or even in the normal adjusting to different altitudes of varying oxygen content. One way to maintain oxygen delivery even if the blood oxygen content is decreased would be to increase blood flow to the tissues. The chemoreceptor reflex works to ensure sufficient delivery of oxygen when blood gas levels change.

Located near the baroreceptors in structures called the **carotid and aortic bodies** are chemoreceptors that respond to changes in oxygen, carbon dioxide and hydrogen ions (pH) in the blood. When there is a decrease in oxygen, an increase in carbon dioxide or an increase in hydrogen ions, these receptors are stimulated (the reflex circuitry is the same as for the baroreceptor reflex). Stimulation of the chemoreceptors results in an increase in cardiac output, which delivers more blood to the tissues, providing sufficient oxygen while at the same time increasing blood flow to the lungs to provide for

adequate gas exchange. Although this reflex does influence cardiac output, it plays a much greater role in regulating the respiratory system, which will be discussed in a later chapter.

Clinical Note

Another important factor in the regulation of cardiac activity is the level of ions in the extracellular fluids. The generation and conduction of action potentials as well as the movement of calcium ions is crucial to normal functioning of the heart. As we have seen previously, the concentrations of certain ions in the extracellular fluid can have a huge impact on the actions of excitable tissues. Of particular importance is the concentration of potassium in the extracellular fluids. Normal extracellular potassium ion concentrations are 3.5 - 5.0mM. A Concentration of <3.5mM is considered hypokalemia while a concentration of >5mM is considered hyperkalemia. Both conditions can be life threatening. Hyperkalemia results in depolarization of the membrane potential. This affects the electrical activity of the heart and early signs are changes in the ECG, such as tall, peaked T waves, increased duration of the PR interval, and widening of the QRS complex. If left untreated the hyperkalemia can eventually result in a systolic cardiac arrest. Hypokalemia, on the other hand results in hyperpolarization of membranes. The heart muscle cells are particularly sensitive to hypokalemia and severe conditions can result in ventricular arrhythmias and again asystole or cardiac arrest.

Adrenal Medullary Mechanism

As you have previously learned, the adrenal medulla synthesizes and releases epinephrine (also called adrenaline) during times of sympathetic stimulation. Epinephrine can act as an activating ligand on all adrenergic receptors that include beta receptors of the heart and vasoconstricting alpha 1 receptors of blood vessels. Stimulation of the heart will use the mechanisms we saw in the previous section to increase inotropy, lusitropy and chronotropy. This combined with vasoconstriction of blood vessels causes increased blood pressure.

Central Nervous System Ischemic Response

The **central nervous system ischemic response** is an emergency response to very low blood flow. The CNS ischemic response receptors are located in the medulla oblongata and respond to very low blood pressure in the brain (below 50 mm Hg). In response, specific vasomotor center receptors stimulate severe constriction of peripheral blood vessels and very intense heart rate increase in order to increase blood pressure. Thus, for a short period of time, ischemia (lack of blood flow) is compensated for and the CNS is able to function. However, the CNS ischemic response is generally not sufficient to maintain adequate blood flow for very long. Metabolic activity in the brain struggles to continue and death is likely. The CNS ischemic response can be likened to a last-ditch effort to prevent the brain from shutting down during episodes of extremely low blood pressure.

Long-Term Regulation

This section will introduce five long-term blood pressure regulation mechanisms: the renin-angiotensin-aldosterone mechanism, the vasopressin/anti-diuretic hormone (ADH) mechanism, the fluid shift mechanism, stress-relaxation response, and the atrial natriuretic mechanism. Each of these works to change blood pressure by altering blood volume, or vascular smooth muscle tone (dilation or constriction). Unlike, short-term blood pressure regulation that occurs in seconds, long-term regulation can take several minutes, hours or days.

Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism plays a very important and active role in blood pressure regulation on a day-to-day basis. It uses a variety of means, such as water reabsorption in the kidney tubules and vasoconstriction, to

regulate blood pressure.

The Renin-Angiotensin-Aldosterone mechanism centers on the level of the enzyme renin in the blood. **Renin** is produced in the kidney in specialized structures known as the **juxtaglomerular apparatus**. When in the blood, renin cleaves a liver-produced serum zymogen (inert enzyme "waiting" to be activated) known as **angiotensinogen.** The cleaved portion is a protein known as **angiotensin I**. Angiotensin I is then cleaved again by an **angiotensin converting enzyme** (ACE: largely found in the small vessels of the lung) into **angiotensin II**, the final, active form of the original angiotensinogen. Angiotensin II then initiates several simultaneous responses as it diffuses throughout the body.

The first of these responses results when angiotensin II binds to specific receptors on smooth muscle cells in arterioles. The resultant signal cascade results in widespread vasoconstriction. This in turn increases the amount of venous blood which returns to the heart as well as increasing peripheral resistance. These two factors combine to increase blood pressure. The second response occurs when angiotensin II binds to cells in the adrenal cortex prompting the production and release of the hormone **aldosterone**. Aldosterone acts on kidney structures called nephrons where it increases the reabsorption of sodium and chloride ions (reabsorption means moving from the nephron filtrate back to circulating blood). If a hormone called ADH (vasopressin) is present, the increase of Na^+ and Cl^- results in reabsorption of water as well (because the water will follow the net movement of solutes). This prevention of solute and water loss in the urine translates into prevention of blood volume loss. Therefore, blood pressure decreases are minimized because of the manipulation of blood volume. The third and fourth responses initiated by angiotensin II are increased salt appetite and an increased sense of thirst. Increased salt intake means increased water as well, because water follows the net gain of solutes. Increased thirst will raise blood volume directly by virtue of increased water intake.

Ace and ACE II

There are different types of ACE enzymes, mainly ACE and ACE II. The ACE II enzyme converts angiotensin II into angiotensin 1-7. Angiotensin 1-7 has opposite effects as that of angiotensin II, in fact, angiotensin 1-7 protects against high blood pressure. It is the ratio between angiotensin II and angiotensin 1-7 that is most important for physiological health and homeostasis. In 2019, the COVID 19 pandemic was caused by a coronavirus (same family type that causes the common cold), first identified in Wuhan China. In COVID-19, ‘CO’ stands for ‘corona,’ ‘VI’ for ‘virus,’ and ‘D’ for disease and the 19 by the year it was discovered. The COVID 19 virus attaches to the ACE II enzyme, using the binding to the enzyme as an entry point into cells. The binding inactivates the enzyme, disturbing the balance between angiotensin II and angiotensin 1-7, and in people already health compromised, that imbalance can prove devastating.

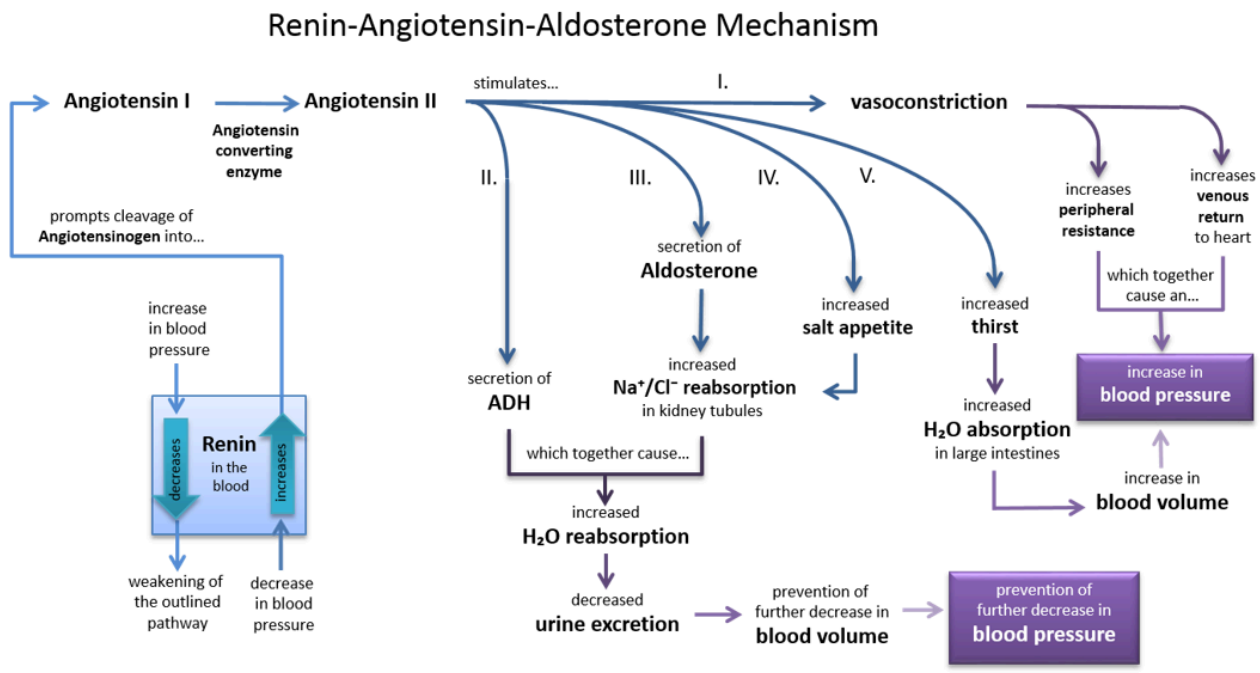


Image drawn by BYUI student Fall 2013

The **vasopressin/anti-diuretic hormone (ADH) mechanism** works side-by-side with the Renin-Angiotensin-Aldosterone mechanism to raise blood pressure. ADH is able to cause vasoconstriction which will increase peripheral resistance. In fact, another name for ADH is vasopressin because of its ability to constrict vessels of the vascular system. However, its main effect is to increase water reabsorption from the kidney nephrons, thus the other name "ADH" which means Anti-Diuretic Hormone. Diuresis means an increase production and excretion of urine. The ADH reflex is activated by two specific indicators: high blood osmolality and low blood pressure.

Fluid Shift Mechanism

The **fluid shift mechanism** is a simple yet very effective means of long-term blood pressure regulation. When blood pressure is high, the amount of interstitial fluid increases, which lowers blood volume. When blood pressure is low, the amount of interstitial fluid is decreased to raise the blood volume. This occurs mostly through the capillaries when pressure deviations change the equilibrium balance pointed out in the section on capillary exchange. It is functional in as little as minutes and is maximally effective in a matter of hours. It is an especially important means of compensating for changes that occur during dehydration and hyperosmolarity.

Atrial Natriuretic Mechanism

The **atrial natriuretic mechanism** is powered by **atrial natriuretic hormone** sometimes called (ANH) which is produced in specialized cells of the right atrium of the heart. When blood volume or vasoconstriction causes more blood to return to the right atrium, the atrium is stretched and there is an increase in release of ANH from the atrial cells. As ANH is distributed throughout the body's vasculature, it causes vasodilation. This decreases peripheral resistance and, as a result, lowers the blood pressure. Simultaneously, the atrial natriuretic hormone acts on the kidney tubules to increase the excretion of both sodium and water in the urine. This in turn decreases blood volume.

Stress-Relaxation Response

The final long-term blood pressure regulation mechanism is the **stress-relaxation response**. This response is a simple adjustment of blood vessel smooth muscle tone in the hours following a change in blood pressure. If, for example, blood volume rose by 400 mL, the blood pressure would rise accordingly. To compensate for this, smooth muscles in the walls of the various types of vessels would gradually relax until the blood pressure drops to a safer level. Oppositely,

in the case of a drop in blood volume, vascular smooth muscles would contract gradually in an attempt to raise blood pressure. This change in smooth muscle tone happens automatically even without any nervous system or hormonal regulation. The tendency of smooth muscle to gradually relax under significant tension or gradually contract under very low tension is an intrinsic property of smooth muscle cells.

Shock

Shock is a life-threatening condition that occurs when there is inadequate delivery of blood for body cells to use. There are several different reasons or causes of this. Shock results in such symptoms as rapid heart rate and rapid loss of blood pressure. If both short-term and long-term blood pressure regulation mechanisms fail to solve the problem, shock can result in death. In fact, circulatory shock is one of the most common causes of death. Shock can arise from hemorrhaging (bleeding), which is called **hemorrhagic shock**. It can also result from failure of the heart to pump blood normally (such as in the case of a heart attack, irregular heartbeat, or valve problems), which is called **cardiogenic shock**. It can occur from system vasodilation in response to an extreme allergic reaction to an antigen to which the body has become hypersensitive, which is called **anaphylactic shock**. Sometimes bacterial toxins can trigger widespread vasodilation and increased capillary permeability. When an infection causes this, we refer to it as **Septic Shock**.

There are three stages of shock that a person can go through. The first is called **compensated shock**. Compensated shock is the initial stage in which blood pressure mechanisms seek to bring circulation back into homeostasis. Short-term responses such as the baroreceptor reflex, the CNS ischemic response, and the chemoreceptor reflex accelerate the heart rate and stimulate vasoconstriction. Long-term responses further cause vasoconstriction and attempt to increase blood volume.

If these attempts fail, circulatory shock advances into a dangerous positive-feedback cycle where heart rate increases steadily without any improvement in blood flow. This is called **progressive shock**. In this stage, blood pressure becomes so low that the body tissues including the heart begins to die. This is due to hypoxia as well as from toxins released from dying cells. Vasodilation increases due to loss of sympathetic nervous function. Capillaries begin to degenerate and become more permeable. This causes a larger net movement of solutes and water into the tissues. Widespread tissue deterioration follows. In this stage, medical intervention may restore a person to homeostasis. Known as **replacement therapy**, this can consist of two types of intervention: introduction of fluids (such as blood transfusion, isotonic saline solutions, etc.) and administration of vasoconstriction drugs. However, once the brain, heart, blood vessels, and tissues have deteriorated to such a point that they can no longer regain normal function or respond to medical intervention, the person is in a stage known as **irreversible shock**. After this threshold has been passed, death is imminent.