Pathophysiology of circulatory shock and Hypertension-7

Circulatory shock

• Circulatory shock means generalized inadequate blood flow through the body to the extent that the body tissues are damaged, especially because too little oxygen and other nutrients are delivered to the tissue cells, even the cardiovascular system itself.

• Shock usually results from **inadequate cardiac output**.

• Therefore, any condition that reduces the cardiac output far below normal may lead to circulatory shock.

Two types of factors can severely reduce cardiac output:

• **Cardiac abnormalities** that decrease the ability of the heart to pump blood.

- These abnormalities include myocardial infarction, severe heart valve dysfunction, heart arrhythmias, and other conditions.
- The circulatory shock that results from diminished cardiac pumping ability is called **cardiogenic shock**.
- as many as 70% of people who experience cardiogenic shock do not survive.
- Factors that **decrease venous return** also decrease cardiac output because the heart cannot pump blood that does not flow into it.
- The most common cause of decreased venous return is **diminished blood volume**,
- but venous return can also be reduced as a result of **decreased vascular tone**, especially of the venous blood reservoirs,
- • or **obstruction to blood flow** at some point in the circulation, especially in the venous return pathway to the heart.

• Occasionally, **cardiac output is normal** or even more than normal, yet the person is **in a state of circulatory shock**.

- This situation can result from situations such as excessive metabolic rate, so even a normal cardiac output is inadequate.
- Whatever the cause of shock, all of them lead to inadequate delivery of nutrients to critical tissues and critical organs, as well as inadequate removal of cellular waste products from the tissues.
- • **Hypovolemia** means diminished blood volume.
- • Hemorrhage is the most common cause of hypovolemic shock.
- • Hemorrhage decreases the filling pressure of the circulation and, as a consequence, decreases venous return. As a result, the cardiac output falls below normal, and shock may ensue.
- • effects on cardiac output and arterial pressure of removing blood from the circulatory system over a period of about 30 minutes.
- • About 10% of the total blood volume can be removed with almost no effect on arterial pressure or cardiac output, but greater blood loss usually diminishes the cardiac output first and later the arterial pressure, both of which fall to zero when about 40% to 45% of the total blood volume has been removed**.**

- This second plateau results from activation of the **central nervous system ischemic response**, which causes extreme stimulation of the sympathetic nervous system when the brain begins to experience lack of O2 or excess buildup of CO2.

- This effect of the central nervous system ischemic response can be called the **"last-ditch stand"** of the sympathetic reflexes in their attempt to keep the arterial pressure from falling too low**.**
- A special value of the **maintenance of normal arterial pressure**, even in the presence of decreasing cardiac output, is **protection of blood flow through the coronary and cerebral circulations**.
- The **sympathetic stimulation does not cause significant constriction of the cerebral or cardiac vessels**. In addition, in both vascular beds, **local blood flow autoregulation is excellent**, which prevents moderate decreases in arterial,pressure from significantly decreasing their blood flows.
- The **sympathetic reflexes** and increased secretion of **catecholamines by the adrenal medullae** provide rapid help toward bringing about recovery because they become maximally **activated within 30 seconds** to a few minutes after hemorrhage.

- The **angiotensin and vasopressin** mechanisms, as well as the **reverse stress-relaxation** that causes contraction of the blood vessels and venous reservoirs, all **require 10 to 60 minutes to respond completely**, but they aid greatly in increasing the arterial pressure or increasing the circulatory filling pressure, thereby increasing the return of blood to the heart.

- • Finally, readjustment of blood volume by **absorption of fluid from the interstitial spaces and intestinal tract, as well as oral ingestion and absorption of additional quantities of water and salt**, may require from **1 to 48 hours**, but recovery eventually takes place, provided the shock does not become severe enough to enter the progressive stage.

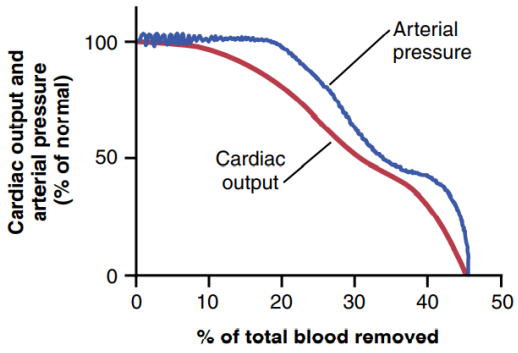
Circulatory shock and BP

- **Arterial pressure** level sometimes is considered the principal **measure of adequacy of circulatory function**. However, the arterial pressure can often be seriously misleading.
- At times, a person may be in severe shock and still have an almost normal arterial pressure because of powerful nervous reflexes that keep the pressure from falling.
- At other times, the arterial pressure can fall to half of normal, but the person still has normal tissue perfusion and is not in shock.

Stages of Circulatory shock

- Because the characteristics of circulatory shock change with different degrees of severity, shock is often divided into the following three major stages:
- 1. A **nonprogressive stage** (sometimes called the **compensated** stage), in which the normal circulatory compensatory mechanisms eventually cause full recovery without help from outside therapy.
- 2. A **progressive stage**, in which, without therapy, the shock becomes steadily worse until death occurs.
- 3. An **irreversible stage**, in which the shock has progressed to such an extent that all forms of known therapy are inadequate

to save the person's life even though, for the moment, the person is still alive.



- **Sympathetic reflex compensation in shock**
- In the absence of the sympathetic reflexes, only 15% to 20% of the blood volume can be removed over a period of 30 minutes before a person dies; in contrast, a person can sustain a 30% to 40% loss of blood volume when the reflexes are intact.
- Therefore, these **reflexes extend the amount of blood loss that can occur without causing death** to about twice that which is possible in their absence.

Circulatory shock (BP and CO)

- The **arterial pressure is maintained** at or near normal levels in the hemorrhaging person **longer than is the cardiac output**.
- The reason for this difference is that the **sympathetic reflexes** are geared more for maintaining arterial pressure than for maintaining cardiac output.
- They increase the arterial pressure mainly by increasing the total peripheral resistance, which has no beneficial effect on cardiac output. However, the sympathetic constriction of the veins is important to keep venous return and cardiac output from falling too much, in addition to their role in maintaining arterial pressure.

Nonprogressive or compensated shock

• If shock is not severe enough to cause its own progression, the person eventually recovers.

- It is called nonprogressive shock or compensated shock, meaning that the sympathetic reflexes and other factors compensate enough to prevent further deterioration of the circulation.
- The factors that cause a person to recover from moderate degrees of shock are the **negative feedback control mechanisms** of the circulation that attempt to return cardiac output and arterial pressure back to normal.

Negative feedback mechanisms in shock

• 1. **Baroreceptor reflexes**, which elicit powerful sympathetic stimulation of the circulation

• 2. **CNS ischemic response**, which elicits even more powerful sympathetic stimulation throughout the body but is not activated significantly until the arterial pressure falls below 50 mm Hg.

• 3. **Reverse stress-relaxation** of the circulatory system, which causes the blood vessels to contract around the diminished blood volume so that the blood volume that is available more adequately fills the circulation.

- 4. **Increased secretion of renin** by the kidneys and formation of angiotensin II, which constricts the peripheral arterioles and also causes decreased output of water and salt by the kidneys.
- 5. **Increased secretion of vasopressin (ADH)**, which constricts the peripheral arterioles and veins and greatly increases water retention by the kidneys.
- 6. **Increased secretion by the adrenal medullae of epinephrine and norepinephrine**, which constricts the peripheral arterioles and veins and increases the heart rate.

- 7. Compensatory mechanisms that return the blood volume back toward normal, including **absorption of large quantities of fluid from the intestinal tract**, **absorption of fluid into the blood capillaries** from the interstitial spaces of the body, **conservation of water and salt by the kidneys**, and **increased thirst** and **increased appetite for salt.**

Progressive shock

- **Cardiac decompensation**:
  - When the arterial pressure falls low enough, coronary blood flow decreases below that required for adequate nutrition of the myocardium, weakening the heart muscle and decreasing the cardiac output more.
  - Thus, a **positive feedback cycle** has developed, whereby the shock becomes more and more severe.
  - the condition of the person, partly because deterioration of the heart is not severe during the first hour or so of shock, but mainly because the heart has reserve capability that normally allows it to pump 300% to 400% more blood than is required by the body for adequate tissue nutrition.
  - In the latest stages of shock, however, **deterioration of the heart** is probably the **most important factor in the final lethal progression of the shock.**
  - • **Vasomotor Failure**. In the early stages of shock, various circulatory reflexes cause intense activity of the sympathetic nervous system. This activity helps delay depression of cardiac output and especially helps prevent decreased arterial pressure.

- • However, there comes a point when diminished **blood flow to the brain's vasomotor center depresses the center** so much that it, too, becomes progressively less active and, finally, totally inactive.
- • Fortunately, the vasomotor center usually does not fail in the early stages of shock if the arterial pressure remains above 30 mm Hg.

• **Blockage of Very Small Vessels by Sludged Blood**. In time, blockage occurs in many of the very small blood vessels in the circulatory system, and this blockage also causes the shock to progress. The initiating cause of this blockage is sluggish blood flow in the microvessels.

• This **acidic effect**, plus other deterioration products from the ischemic tissues, causes local blood agglutination, resulting in minute blood clots and leading to very small plugs in the small vessels.

• **Increased Capillary Permeability**.

- After many hours of capillary hypoxia and lack of other nutrients, the permeability of the capillaries gradually increases, and large quantities of fluid begin to transude into the tissues.
- Capillary hypoxia does not cause increased capillary permeability **until the late stages of prolonged shock.**

• **Patchy Areas of Tissue Necrosis**

- Caused by Patchy Blood Flows in Different Organs.
- Not all cells of the body are equally damaged by shock because some tissues have better blood supplies than others. For example, the cells adjacent to the arterial ends of capillaries receive better nutrition than cells adjacent to the venous ends of the same capillaries. Therefore, more nutritive deficiency occurs around the venous ends of capillaries than elsewhere.

- **Cardiac Depression Caused by Endotoxin**.
  - Endotoxin is released from the bodies of dead gram-negative bacteria in the intestines. Diminished blood flow to the intestines often causes enhanced formation and absorption of this toxic substance.
  - The circulating toxin then causes increased cellular metabolism, despite inadequate nutrition of the cells, which has a specific effect on the heart muscle, causing cardiac depression.
  - Endotoxin can play a major role in some types of shock, especially **septic shock.**
  - **Release of Toxins by Ischemic Tissue**.
  - Shock has been suggested to cause tissues to release toxic substances, such as histamine, serotonin, and tissue enzymes, that cause further deterioration of the circulatory system.
- **Generalized Cellular Deterioration**.
  - As shock becomes severe, many signs of generalized cellular deterioration occur throughout the body.
  - The **liver** is especially affected mainly because of the lack of enough nutrients to support the normally high rate of metabolism in liver cells, but also partly because of the exposure of the liver cells to any vascular toxin or other abnormal metabolic factor occurring in shock.

  - Among the **damaging cellular effects** that are known to occur in most body tissues are the following:

- 1. Active transport of sodium and potassium through the cell membrane is greatly diminished. As a result, sodium and chloride accumulate in the cells, and potassium is lost from the cells. In addition, the cells begin to swell.
- • 2. Mitochondrial activity in the liver cells, as well as in many other tissues of the body, becomes severely depressed.
- • 3. **Lysosomes in the cells in widespread tissue areas begin to break open**, with intracellular release of hydrolases, which cause further intracellular deterioration.
- • 4. Cellular metabolism of nutrients, such as glucose, eventually becomes greatly depressed in the last stages of shock. The actions of some hormones are depressed as well, including almost 100% depression of the actions of insulin.

- All these effects contribute to further deterioration of many organs of the body, including especially the following:
- (1) the **liver**, with depression of its many metabolic and detoxification functions.
- (2) the **lungs**, with eventual development of pulmonary edema and poor ability to oxygenate the blood.
- (3) the **heart,** thereby further depressing its contractility.

- **Positive Feedback Deterioration of Tissues in Shock and Vicious Cycle of Progressive Shock**.

- All the factors that can lead to further progression of shock are types of positive feedback—that is, each increase in the degree of shock causes a further increase in the shock.

- However, positive feedback does not necessarily lead to a vicious cycle. Development of a vicious cycle depends on the intensity of the positive feedback.

- In severe shock, however, the deteriorative feedback mechanisms become more and more powerful, leading to such rapid deterioration of the circulation that all the normal negative feedback systems of circulatory control acting together cannot return the cardiac output to normal.
- That's why there is a **critical cardiac output level** above which a person in shock recovers and below which a person enters a vicious cycle of circulatory deterioration that proceeds,until death.
- ***Irreversible shock***
- After shock has progressed to a certain stage, transfusion or any other type of therapy becomes incapable of saving the person's life. The person is then said to be in the irreversible stage of shock.
- Ironically, even in this irreversible stage, therapy can, on rare occasions, return the arterial pressure and even the cardiac output to normal or near normal for short periods.

Hypovolemic shock caused by plasma loss

- Severe plasma loss occurs in the following conditions:
- 1. **Intestinal obstruction** may cause severely reduced plasma volume. Distention of the intestine in intestinal obstruction partly blocks venous blood flow in the intestinal walls, which increases intestinal capillary pressure, causing fluid to leak from the capillaries into the intestinal walls and intestinal lumen. reduced total blood plasma protein, as well as reduced plasma volume.
- 2. **Severe burns** cause loss of plasma so that the plasma volume becomes markedly reduced.

- Loss of fluid from all fluid compartments of the body is called **dehydration;** Some of the causes of this type of shock are the following:
- (1) excessive sweating
- (2) fluid loss in severe diarrhea or vomiting
- (3) excess loss of fluid by the kidneys
- (4) inadequate intake of fluid and electrolytes
- (5) destruction of the adrenal cortices, with loss of aldosterone secretion and consequent failure of the kidneys to reabsorb sodium, chloride, and water, which occurs in the absence of the adrenocortical hormone aldosterone.

Hypovolemic shock caused by trauma

- One of the most common causes of circulatory shock is trauma to the body.
- Often, the shock results simply from hemorrhage caused by the trauma, but it can also occur even **without hemorrhage because extensive contusion** of the body can damage the capillaries sufficiently to allow excessive loss of plasma into the tissues.
- This phenomenon results in greatly reduced plasma volume,with resultant hypovolemic shock.

- ***Neurogenic shock***

• **Shock** occasionally occurs **without any loss of blood volume**.

- • Instead, the **vascular capacity increases so much** that even the normal amount of blood is incapable of filling the circulatory system adequately.
- • One of the major causes of this condition is **sudden loss of vasomotor tone** throughout the body, resulting especially in **massive dilation of the veins**.
- • increase in vascular capacity reduces the mean systemic filling pressure, which reduces venous return to the heart. Diminished venous return caused by vascular dilation is called **venous pooling of blood**.

- ***Causes of Neurogenic Shock***:
- 1. **Deep general anesthesia** often depresses the vasomotor center enough to cause vasomotor paralysis.
- 2. **Spinal anesthesia**, especially when this extends all the way up the spinal cord, blocks the sympathetic nervous outflow from the nervous system.
- 3**. Brain damage** is often a cause of vasomotor paralysis. Many patients who have had a brain concussion or contusion of the basal regions of the brain.

Anaphylactic shock

• Anaphylaxis is an **allergic condition** in which cardiac output and arterial pressure often decrease drastically.

- It results primarily from an antigen-antibody reaction that rapidly occurs after an antigen to which the person is sensitive enters the circulation.
- One of the principal effects is to cause the basophils in the blood and mast cells in the pericapillary tissues to release,histamine or a histamine-like substance.

- ***The histamine causes the following:***
- (1) an increase in vascular capacity because of venous dilation, thus causing a marked decrease in venous return;
- (2) dilation of the arterioles, resulting in greatly reduced arterial pressure;
- (3) greatly increased capillary permeability, with rapid loss of fluid and protein into the tissue spaces.
- The net effect is a great reduction in venous return and, sometimes, such serious shock that the person may die within minutes.

Septic shock

• Septic shock refers to a **bacterial infection widely disseminated to many areas of the body**, with the infection being **carried through the blood** from one tissue to another and causing extensive damage.

- There are many varieties of septic shock because of the many types of bacterial infections that can cause it, and because infection in different parts of the body produces different effects.
- Most cases of septic shock, however, are caused by Gram-positive bacteria, followed by endotoxin-producing Gram negative bacteria.
- Septic shock is extremely important to the clinician because, other than cardiogenic shock, septic shock is currently **the most frequent cause of shock-related death in the hospital**.

- **Some of the typical causes of septic shock include the following:**
- 1. **Peritonitis** caused by spread of infection from the uterus and fallopian tubes, sometimes resulting from an instrumental abortion performed under unsterile conditions.
- 2. **Peritonitis** resulting from rupture of the gastrointestinal system, sometimes caused by intestinal disease or by wounds.
- 3. **Generalized** bodily infection resulting **from spread of a skin** infection such as streptococcal or staphylococcal infection
- 4. **Generalized gangrenous infection** resulting specifically from gas gangrene bacilli, spreading first through peripheral tissues and finally via the blood to the internal organs, especially the liver
- 5. Infection spreading into the blood **from the kidney or urinary tract**, often caused by colon bacilli.

- ***The following features are often observed:***
- 1. High fever
- 2. Often marked vasodilation throughout the body, especially in the infected tissues

- 3. High cardiac output in perhaps half of patients, caused by arteriolar dilation in the infected tissues and by high metabolic rate and vasodilation elsewhere in the body, resulting from bacterial toxin stimulation of cellular metabolism and from a high body temperature
- 4. Sludging of the blood, caused by red cell agglutination in response to degenerating tissues
- 5. Development of micro–blood clots in widespread areas of the body, a condition called disseminated intravascular coagulation (DIC); also, this causes the blood clotting factors to be used up,so hemorrhaging occurs in many tissues.
- • In early stages of septic shock, the patient usually does not have signs of circulatory collapse but only signs of the bacterial infection.
- • As the infection becomes more severe, the circulatory system usually becomes involved because of direct extension of the infection or secondarily as a result of toxins from the bacteria, with resultant loss of plasma into the infected tissues through deteriorating blood capillary walls.

Management of shock

- Replacement therapy:
- **Blood and Plasma Transfusion**.
- If a person is in shock caused by hemorrhage, the best possible therapy is usually transfusion of whole blood.
- If the shock is caused by plasma loss, the best therapy is administration of plasma.

- When dehydration is the cause, administration of an appropriate electrolyte solution can correct the shock.
- Whole blood is not always available. Plasma can usually substitute adequately for whole blood because it increases the blood volume and restores normal hemodynamics. Plasma cannot restore a normal hematocrit, but the body can usually stand a decrease in hematocrit to about half of normal before serious consequences result if cardiac output is adequate. Therefore, in emergency conditions, it is reasonable to use plasma in place of whole blood for treatment of hemorrhagic or most other types of hypovolemic shock.
- Sometimes, plasma is unavailable. In these cases, various plasma substitutes have been developed that perform almost exactly the same hemodynamic functions as plasma. One of these substitutes is dextran solution.

• **Dextran Solution as a Plasma Substitute**. The principal requirement of a truly effective plasma substitute is that it remain in the circulatory system— that is, it does not filter through the capillary pores into the tissue spaces.

- In addition, the solution must be nontoxic and must contain appropriate electrolytes to prevent derangement of the body's extracellular fluid electrolytes on administration.
- To remain in the circulation, the plasma substitute must contain some substance that has a large enough molecular size to exert colloid osmotic pressure.
- Treatment by the **Head-Down Position**.
- When the pressure falls too low in most types of shock, especially in hemorrhagic and neurogenic shock, placing the patient with the

head at least 12 inches lower than the feet helps in promoting venous return, thereby also increasing cardiac output.

- This head-down position is the first essential step in the treatment of many types of shock.

• **Oxygen Therapy**.

- Because a major deleterious effect of most types of shock is too little delivery of oxygen to the tissues, giving the patient oxygen to breathe can be of benefit in some cases.
- However, this intervention frequently is far less beneficial than one might expect because the problem in most types of shock is not inadequate oxygenation of the blood by the lungs but inadequate transport of the blood after it is oxygenated.

• **Glucocorticoids**—adrenal cortex hormones that control glucose metabolism—are frequently given to patients in severe shock for several reasons:

- (1) experiments have shown empirically that glucocorticoids frequently increase the strength of the heart in the late stages of shock;
- (2) glucocorticoids stabilize lysosomes in tissue cells and thereby prevent the release of lysosomal enzymes into the cytoplasm of the cells, thus preventing deterioration from this source; and
- (3) glucocorticoids might aid in the metabolism of glucose by the severely damaged cells.

- ***Management of neurogenic and anaphylactic shock***
- A **sympathomimetic drug** is a drug that mimics sympathetic stimulation.

- These drugs include **norepinephrine, epinephrine**, and a large number of long-acting drugs that have the same basic effects as epinephrine and norepinephrine.
- In two types of shock, sympathomimetic drugs have proven to be especially beneficial. The first of these is neurogenic shock, in which the sympathetic nervous system is severely depressed.
- Sympathomimetic drugs have not proved to be very valuable in hemorrhagic shock.
- The reason is that in this type of shock, the sympathetic nervous system is almost always maximally activated by the circulatory reflexes; so much norepinephrine and epinephrine are already circulating in the blood that sympathomimetic drugs have essentially no additional beneficial effect.

- ***Circulatory arrest***
  • A condition closely allied to circulatory shock is circulatory arrest, in which **all blood flow stops**.
  • This condition can occur, for example, as a result of cardiac arrest or ventricular fibrillation.
- • **Ventricular fibrillation** can usually be stopped by strong electroshock of the heart**.**
- In the case of complete cardiac arrest, a normal cardiac rhythm can sometimes be restored by immediately applying **cardiopulmonary resuscitation** procedures while at the same time supplying the patient's lungs with adequate quantities of ventilatory oxygen.

• A special challenge in circulatory arrest is to **prevent detrimental effects of the arrest on the brain**.

- In general, more than 5 to 8 minutes of total circulatory arrest can cause at least some degree of permanent brain damage in

more than half of patients. Circulatory arrest for as long as 10 to 15 minutes almost always permanently destroys significant amounts of mental capacity.

- For many years, it was thought that this detrimental effect on the brain was caused by the acute cerebral hypoxia that occurs during circulatory arrest. However, experiments have shown that if blood clots are prevented from occurring in the blood vessels of the brain, this will also prevent much of the early deterioration of the brain during circulatory arrest.

Pathophysiology of Hypertension*

• **The Role of the Kidney and Body Fluid Volumes in Hypertension**

• 1. **the production of renin**:

• Renin is the rate-limiting step for activation of the circulating renin- angiotensin system (RAS) and its synthesis and secretion by the kidney is tightly regulated.

2. Reset or alter the pressure diuresis and natriuresis.

- Translocation of transporters and change of function, in addition to upregulation of receptors.
- That can be mediated by Ang II, inflammatory cytokines, loss of NO, and adrenergic stimulation.
- Shifts in pressure natriuresis are often not reflected by overt changes in renal function as measured by usual clinical parameters.
- 3. modulate systemic sympathetic tone by generating reflex signals via renal afferent nerves.
- The ability of renal afferent nerves to initiate an increase in global sympathetic outflow.

- 4. A fourth important role of the kidney in hypertension is to serve as a site of immune activation.

- The Role of the **Vasculature** in Hypertension:
- 1. Enhanced milieu of vasoconstrictor hormones, including Ang II, catecholamines, and vasopressin, coupled with alterations in vascular function that promote vasoconstriction and diminish vasodilatation.
- Hypertension is also associated with impaired vasodilatation.

  Endothelium-dependent vasodilatation and NO signaling are reduced in hypertension.
- • 2. Perturbations of both microvascular and large vessel structure represent a second vascular contribution to hypertension.
- • Hypertrophy of vascular wall, narrowing of the lumen, arterial stiffness of large arteries, changes in the extracellular matrix...
- 3. there is an impaired vessel wall defense against thrombosis in hypertension that has been related to increased endothelial expression of tissue factor and the vascular cell adhesion molecule 1.
- 4. A fourth role of the vasculature in hypertension is to serve as a source and target of immune activation.
- This is in part mediated by a cross-talk between the endothelium and immune cells.
- The Central Nervous System in Hypertension.
- Aldosterone and Mineralocorticoid receptors.
- Inflammatory and immune mechanisms.

- ROS.

Goodluck, Rayyan shtewe ☺.