UNIT 4: THE CIRCULATION

FROM GUYTON AND HALL TEXTBOOK

BY FATIMA HAIDER

KGMC

- **VOLUME OF BLOOD IN DIFFERENT PARTS OF CIRCULATION**
  1. Systemic circulation – 84%
  2. Heart and lungs – 16%
     Heart – 7%
     Pulmonary vessels – 9%
  3. Veins – 64%
  4. Arteries – 13%
  5. Arterioles and capillaries – 7%

- **v =** $\frac{F}{A}$
  v: velocity of blood flow
  F: Blood flow
  A: cross-sectional area of vessel

- Velocity of blood flow in
  Aorta = 33cm/s
  Capillaries – 0.3mm/s

- **Mean Pressure in**
  Aorta = 100 mmHg
  Arteries = Systolic 120 mmHg
  Diastolic 80 mmHg
  Mean arterial pressure = 93 mmHg
  Vena Cava = 0 mmHg
  Capillaries (near arteriolar end) = 35 mmHg
  Capillaries (near venous ends) = 10 mmHg
  Capillaries (Average pressure) = 17 mmHg
  Glomerular capillaries = 60 mmHg
  Pulmonary artery = systolic 25 mmHg
  Diastolic 8 mmHg
  Mean pulmonary arterial pressure = 16 mmHg
  Mean pulmonary capillary pressure = 7 mmHg

- **Blood Flow =** $\frac{\Delta P}{R}$
  F: blood flow
  ΔP= pressure difference ($P_1 - P_2$) between two ends of vessel
  R: resistance (vascular resistance)

- Cardiac output = 5000ml/min or 5L/min

- **Reynold's number** is the measure of tendency for turbulence (turbulent flow of blood in a vessel) to occur
  Re = $\frac{vd\rho}{\eta}$
  Re: Reynold's number
  v: mean velocity of blood flow (in cm/s)
  d: vessel diameter
  ρ= density (grams/ml)
  η= vicosity (in poise)

- Viscosity of blood = 1/30 poise
  Density of blood is slightly greater than 1

- When Reynold's number rises above 200 to 400, turbulent flow will occur at some branches of vessels but will die out along the smooth portions of the vessels.
  When Reynold's number rises above approximately 2000, turbulence will usually occur, even in a straight, smooth vessel

- Conductance of vessel increases in proportion to the fourth power of the diameter
  Conductance $\propto$ Diameter^4

- **Poiseuille's Law**
  F = $\frac{\pi \Delta P r^4}{8\eta l}$
  F: Rate of blood flow
  ΔP: pressure difference between ends of a vessel
  r: radius of vessel
  η: viscosity of blood
  l: length of vessel

- Total resistance of vessels arranged in series
  $R_{TOTAL} = R_1 + R_2 + R_3$…….

- Total Resistance of vessels arranged in parallel

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

For a given pressure gradient, far greater amounts of blood will flow through parallel system than through any of the individual blood vessels.

- The viscosity of normal blood is about three times as great as the viscosity of water.
- The viscosity of blood at a normal hematocrit is about 3 to 4
- The viscosity of blood plasma is about 1.5 times that of water
- Law of Laplase

  T = ΔP x (r/h)

  T: wall tension
  ΔP: transmural pressure gradient
  r: radius of blood vessel
  h: wall thickness

- **Vascular Distensibilty =** $\frac{Increase\ in\ volume}{(Increase\ in\ pressure)\ (Original\ volume)}$
- The veins, or average, are about 8 times more distensible than the arteries. It means given increase in pressure causes about 8 times as much increase in blood in vein as in an artery of comparable size
- The pulmonary arteries normally operate under pressures about one-sixth of those in systemic arterial system, and their distensibilities are correspondingly greater- about six times the distribution of systemic arteries
- **Vascular compliance =** $\frac{Increase\ in\ volume}{Increase\ in\ pressure}$

  Vascular compliance indicate the total quantity of blood that can be stored in a given portion of circulation for each mmHg pressure rise
- **Compliance = Distensibilty x Volume**

  The compliance of a systemic vein is about 24 times that of corresponding artery because it is about 8 times as distensible and has volume about 3 times as great (8 x 3 = 24)
- The difference between systolic and diastolic pressure is called **pulse pressure**

  Pulse pressure = 120 – 80 = **40mmHg**
- **Pulse pressure depends on:**

1. Stroke volume output of the heart – Greater stroke volume output, greater the pulse pressure
2. Compliance (total distensibility) of arterial tree – the less the compliance, the greater the pulse pressure

- The pulse pressure in old age sometimes rises to twice normal because the arteries have stiffened with arteriosclerosis and therefore are relatively non-compliant

- **Pulse pressure** $\approx \frac{\boldsymbol{Stroke\ volume}}{\boldsymbol{Arterial\ compliance}}$
  - Aortic valve stenosis - decreased pulse pressure due to decreased stroke volume
  - Patent ductus arteriosus – increased pulse pressure due to decreased diastolic pressure
  - Aortic regurgitation – increased pulse pressure due to decreased aortic pressure (systolic pressure)

- Pressure in right atrium is called **central venous pressure** as blood from all systemic veins flow into the right atrium

- **Auscultatory method from finding blood pressure**
  - Systolic pressure noted as soon as Korotkoff sounds are heard
  - Diastolic pressure noted as soon as Korotkoff sounds disappear completely
  - In patients with arteriovenous fistulas for hemodialysis or with aortic insufficiency, Korotkoff sounds may be heard even after complete deflation of the cuff

- Right atrial pressure is regulated by a balance between
  1. Ability of heart to pump blood out of the right atrium and ventricle into the lungs
  2. Venous return

- Factors that increase **venous return** and thereby increase right atrial pressure are:
  1. Increased blood volume
  2. Increased large vessel tone throughout the body with resultant increased peripheral venous pressures
  3. Dilation of arterioles, which describes the peripheral resistance and allows rapid flow of blood from arteries into veins

- The normal right atrial pressure is 0 mmHg
  It can increase to 20 – 30 mmHg under very abnormal condition, such as
  1. Serious heart failure
  2. After massive transfusion of blood, which greatly increase venous return

- **Pressure in vessels throughout the body in standing still person**
  Right atrium = 0 mmHg

Veins of feet = +90 mmHg
Subclavian vein = +6 mmHg
Veins of hand = +35 mmHg
Neck veins = 0 mmHg
Veins inside skull (in sagittal sinus) = -10 mmHg

- 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 heart and death.

- Under normal circumstances, the venous pressure in the feet of walking adult remains less than +20 mmHg

- In sitting position, the neck veins are never distended in the normal, quietly resting person.
    - When right atrial pressure increases to +10 mmHg, the lower veins of neck begin to protrude
    - When right atrial pressure increases to +15 mmHg, all the veins in the neck become distended

- **Specific blood reservoirs**
    1. Spleen
    2. Liver
    3. Large abdominal veins
    4. Venous plexus beneath the skin
    5. Heart
    6. Lungs

- The red pulp of the spleen is a special reservoir that contains large quantities of red blood cells.

- Diameter of arterioles = 10 – 15 μm
  Diameter of capillaries = 4 – 9 μm

- Thickness of capillary wall = 0.5 μm

- **Capillary wall composed of**
    1. Unicellular layer of endothelial cells
    2. A thin basement membrane on outside of capillary

- In capillaries, intercellular cleft is a channel having gap junctions and tight junctions, between two endothelial cells through which molecules travel.

- **Caveoli**

- Minute plasmalemmal (related to plasma membrane) vesicles
- Formed from oligomers of caveolins (protein) that are associated with molecules of cholesterol and sphingolipids
- May play a role in endocytosis
- Role in transcytosis of macromolecules across the interior of endothelial cells

- Special pores in capillaries of different organs
  - Brain – tight junctions in pores
  - Liver – pores almost wide open
  - Gastrointestine – pores midway in size between those of muscles and liver
  - Glomerular capillaries have fenestrae for filtration

- **Vasomotion** – intermittent contraction of the meta-arterioles and pre-capillary sphincters. Oxygen deficit in tissues causes increased vasomotion.

- Lipid soluble substances (CO_2, O_2) diffuse directly through the cell membrane of capillary endothelium.
  Water soluble substances (H_2O, Na^+, Cl^-, glucose) diffuse through intercellular pores in the capillary membrane.

- Width of capillary intercellular cleft pores = 6 – 7 nm

- About one-sixth of the total volume of the body consist of spaces between cells, which collectively are called the interstitium. The fluid in these spaces is called the interstitial fluid.

- **Structure of interstitium** composed of:
  1. Collagen fiber bundle
  2. Proteoglycan filaments (98% hyaluronic acid and 2% protein)

- **Interstitial fluid**
  1. Tissue gel consisting of
     - Proteoglycan filaments
     - Trapped fluid between proteoglycan filaments
  2. Free fluid

- **Pressure of capillaries**
  In arterial end – 30 to 40 mmHg
  In middle – 25 mmHg
  In venous end – 10 to 15 mmHg

- **Colloidal osmotic pressure** of normal human plasma = 28 mmHg

- By dissolved proteins – 19 mmHg
- By Donan effect – 9 mmHg

- **Contribution to total colloidal osmotic pressure of plasma by**
  - Albumins – 80%
  - Globulins – 20%
  - Fibrinogen – none

- Average protein concentration of interstitial fluid of most tissues is only 40% of that in plasma

- Average interstitial fluid colloidal osmotic pressure for this concentration of proteins is about 8 mmHg

- The normal rate of net filtration in the entire body, not including the kidneys, is only about 2ml/min

- **Vasodilator theory** – The greater the rate of metabolism or the less the availability of oxygen or some other nutrients to the tissue, the greater the rate of formation of vasodilator substances in the tissue cells.

- **Vasodilator substances –** Adenosine, CO_2, adenosine phosphate compounds, histamine, K^+ ions, H^+ ions

- Vasodilation occurs in beriberi, in which the patient has deficiencies of Vitamin B substances thiamine, niacin, and riboflavin. In this disease, the peripheral vascular blood flow almost everywhere in the body after increases twofold to threefold. As all these vitamins are necessary for oxygen-induced phosphorylation, which is required to produce ATP in tissue cells, so deficiency of these vitamins leads to diminished smooth muscle contractile ability and therefore local vasodilation as well.

- **Reactive hyperemia** occurs when a tissue is unblocked after being blocked for some time (few seconds to an hour)

- **Active hyperemia** occurs when tissue metabolic rate increases

- Endothelium-derived vasodilator – Nitric oxide
  Endothelium-derived vasoconstrictor – endothelin

- **Nitric oxide (NO)**

- After diffusing out of endothelial cells, nitric oxide has a half-life in blood of only about 6 seconds and acts mainly in local tissues where it is released
- Nitric oxide is released in response to
  1. Increased stress on vessel walls due to increased blood flow
  2. Stimulated by some vasoconstrictors such as Angiotensin II. The increase NO release protects against excessive vasoconstriction
- When endothelial cells are damaged by chronic hypertension or atherosclerosis, impaired NO synthesis may contribute to excessive vasoconstriction and worsening of hypertension and endothelial damage. If untreated, this may eventually cause vascular injury and damage to vulnerable tissues such as heart, kidneys and brain.

- **Angiogenesis** is the formation of new blood vessels

- **Factors that increase growth of new blood vessels:**
  1. Vascular endothelial growth factor (VEGF)
  2. Fibroblast growth factor
  3. Platelet derived growth factor (PDGF)
  4. Angiogenin

- **Inhibitors of Angiogenesis**
  1. Angiostatin
  2. Endostatin

- **Inward eutrophic remodeling** is seen in essential hypertension and is associated with an increase in wall thickness and a reduction in lumen diameter.
  Hypertrophic remodeling involves an increase in wall thickness and a reduction in lumen diameter.
  Outward remodeling is an increase in vessel size and hypertrophy of the vessel's smooth muscle cells which often occurs when a large vein (often the saphenous vein) is implanted in a patient for a coronary artery bypass graft procedure.
  Outward hypertrophy remodeling is an increase in wall thickness, lumen diameter and cross-sectional area of vascular wall.

- A **fistula** is an abnormal connection between two body parts, such as an organ or blood vessel and another structure

- In dialysis patients, an atrioventricular fistula is created between radial artery and antecubital vein of the forearm to permit vascular access for dialysis.
  Due to this fistula, the blood flow rate in the radial artery may increase as much as 10 to 50 times the normal flow rate. As a result of high flow rate and high shear stress on vessel wall,

outward remodeling occurs in radial artery while outward hypertrophic remodeling occurs in venous side of fistula.

- **Local vasoconstrictors**
  1. Epinephrine
  2. Nor-epinephrine
  3. Angiotensin II
  4. Vasopressin or ADH

- **Local vasodilators**
  1. Bradykinin
  2. Histamine

- Nor-epinephrine is more powerful vasoconstrictor than epinephrine.
  In some tissues, epinephrine can cause vasodilation. A special example of vasodilation caused by epinephrine is that which occurs in coronary arteries during increased heart activity.

- Angiotensin II is a powerful vasoconstrictor that cause constriction of many arterioles to increase the total peripheral resistance, and decrease sodium and water excretion by the kidneys thereby increasing arterial pressure

- Vasopressin is the body's most potent vasoconstrictor

- **<u>Vascular control by ions and many other chemical factors</u>**
  - Increase in intracellular Ca^{+2} ions concentration cause vasoconstriction as calcium stimulate smooth muscle contraction
  - Increase in K^{+} or Mg^{+2} ions concentration cause vasodilation as these ions inhibit smooth muscle contraction
  - Increased H^{+} ion concentration (decreased pH) cause arteriolodilation
    Decreased H^{+} ion concentration (increased pH) cause arterioloconstriction
  - Anions as acetate and citrate cause vasodilation
  - CO_2 acts as vasodilator

- **Sympathetic vasomotor nerves fibers originate from:**
  - $T_1 – T_{12}$
  - L_1 and L_2

- In most tissues, all vessels except capillaries have sympathetic innervation

- **Vasomotor center in the brain transmits:**
  1. Parasympathetic impulses through the vagus nerve to the heart

2. Sympathetic impulses through spinal cord and peripheral sympathetic nerves to virtually all arteries, arterioles and veins of the body

- Important areas in vasomotor center of brain
  1. **Vasocontrictor area** – excite preganglionic vasoconstrictor neurons of the sympathetic nervous system
  2. **Vasodilator area** – inhibits vasoconstrictor area
  3. **Sensory area located in tractus solitarius** – receives nerve signals from vagus and glossopharyngeal nerves and helps control activities of vasoconstrictor and vasodilator areas.

- **Sympathetic vasoconstrictor tone:** Continual firing of sympathetic vasoconstrictor nerve fibers is called sympathetic vasoconstrictor tone which maintain a partial state of constriction in blood vessels, called vasomotor tone.

- **To raise arterial pressure:**
  1. Most arterioles of systemic circulation are constricted
  2. Veins are strongly constricted
  3. Heart is directly stimulated by the autonomic nervous system, further enhancing cardiac pumping

- The best known of the nervous mechanisms for arterial pressure control is **baroreceptor reflex**
  - Baroreceptors present in walls of large systemic arteries
  - Rise in arterial pressure stretches baroreceptors and cause them to transmit signals to CNS
  - Feedback signals sent back through autonomic nervous system to circulation to reduce arterial pressure back to normal

- Baroreceptors respond much more to a rapidly changing pressure than to a stationary pressure

- Excitation of baroreceptors by high pressure causes:
  1. Vasodilation of veins and arterioles throughout the peripheral circulatory system
  2. Decreased heart rate and strength of heart contraction

- Chemoreceptor cells are sensitive to low oxygen or elevated CO_2 and hydrogen ion levels

- **Chemoreceptor** is not a powerful arterial pressure controller until the arterial pressure falls below 80mmHg. Therefore, it is at lower pressure that this reflex becomes important to help prevent further decrease in arterial pressure

- The atria and pulmonary arteries have stretch receptors in their walls called **low-pressure receptors.**
  These low-pressure receptors minimize arterial pressure changes in response to changes in blood volume.

- Stretch of atria due to increased volume cause activation of low-pressure atrial receptors which causes:
  1. Reflex reductions in renal sympathetic nerve activity
  2. Decreased tubular re-absorption
  3. Dilation of afferent arterioles in the kidneys
  4. Decreased secretion of ADH from hypothalamus
  5. Release of atrial natriuretic peptide (to aid excretion of sodium and water in urine)
     These mechanisms tend to return blood volume back to normal

- **Increase in blood volume stimulates**:
  1. Baroreceptor reflex ⎫ increase sodium and
  2. Atrial volume reflex ⎭ water retention
  3. Bainbridge reflex ⎫ increase heart rate

- **Bainbridge reflex** – increased atrial pressure increases heart rate

- **CNS ischemic response** occurs when blood flow to vasomotor center decrease severely enough to cause nutritional deficiency i.e. cause cerebral ischemia. In response vasoconstrictor and cardioaccelerator neurons in vasomotor center become strongly excited and can elevate arterial pressure dramatically, sometimes as high as 250mmHg for as long as 10 minutes.
  The CNS ischemic response is one of the most powerful of all activators of sympathetic vasoconstrictor system.

- **Cushing Reaction** is a special type of CNS ischemic response that result from increased pressure of cerebrospinal fluid around the brain in the cranial vault.

- **Abdominal compression reflex** – In response to low arterial pressure and stimulation from baroreceptor and chemoreceptor reflex leads to abdominal muscle contractions that compress all venous reservoirs of abdomen and halps translocate blood towards heart

- Skeletal muscle contraction increases cardiac output and arterial pressure during exercise

- In humans an increase in arterial pressure of only a few mm of Hg can double the renal output of water, a phenomenon called **pressure diuresis**, as well as double the output of salt, called **pressure natriuresis**.

Arterial Pressure	Urinary output
50 mmHg	Zero
100 mmHg	Normal
200 mmHg	4 to 6 times normal

- Chronic increase in arterial pressure
  1. Acts on kidney to increase excretion
  2. Cause decreased activity of sympathetic nervous system, partly through baroreceptor system
  3. Reduce formation of Angiotensin II and aldosterone thereby increasing salt and water excretion

- Decrease in arterial pressure leads to:
  1. Activation of sympathetic nervous system
  2. Formation of antinatriuretic hormones i.e. Angiotensin II and aldosterone is increased

- In **salt-insenstive people**, large variations in salt intake do not change blood pressure more than a few mmHg

- In **salt-sensitive people**, even moderate increase in salt intake may cause significant increase in arterial pressure. This may be seen in people with kidney injury or excessive secretion of anti-natriuretic hormones

- It is the increase in renal resistance, not total peripheral resistance that causes increase in arterial pressure.

- A mean arterial pressure greater than 110 mmHg (normal is ≈ 90mmHg) is considered to be hypertensive. This level of mean pressure occurs when the diastolic blood pressure is greater than 90 mmHg and systolic blood pressure is greater than 135 mmHg

- **Lethal effects of hypertension are:**
  1. Excess workload on the heart leads to early heart failure and coronary heart disease, often causing death as a result of heart attack.
  2. The high pressure frequently damages a major blood vessel in the brain, followed by death of major portions of the brain; this occurrence is a *cerebral infarct*. Clinically, it is called a *stroke*. Depending on which part of the brain is involved, a stroke can be fatal or cause paralysis, dementia, blindness, or multiple other serious brain disorders.

3. High pressure almost always causes injury in the kidneys, producing many areas of renal destruction and, eventually, kidney failure, uremia, and death.

- Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. Renin is synthesized and stores in the juxtaglomerular cells of the kidneys.

- When arterial pressure falls, the juxtaglomerular cells release renin by the following mechanisms:
  1. Pressure-sensitive baroreceptors in the juxtaglomerular cells respond to decreased arterial pressure with increased release of renin.
  2. Decreased sodium chloride delivery to the macula densa cells in the early distal tubule stimulates renin release
  3. Increased sympathetic nervous system activity stimulates renin release by activating beta-adrenergic receptors in the juxtaglomerular cells. Sympathetic stimulation also activates alpha-adrenergic receptors, which can increase sodium chloride re-absorption and reduce glomerular filtration rate in cases of strong sympathetic activation. Increased renal sympathetic activity also enhances the sensitivity of renal baroreceptor and macula densa mechanisms for renin release.

- Angiotensin II is an extremely powerful vasoconstrictor

- **Effects of Angiotensin II**
  1. Angiotensin II acts directly on kidneys to cause salt and water retention by
     - Constriction of glomerular efferent arterioles
     - Increased tubular reabsorption of sodium and water
  2. Angiotensin II increases kidney salt and water retention by stimulating release of aldosterone from adrenal glands

- **One-Kidney Goldblatt Hypertension**
  - When one kidney is removed and the renal artery in the other kidney is constricted
  - The kidney senses a low blood pressure due to constricted artery and release renin
  - Renin stimulates Angiotensin II and aldosterone which produce a rise in blood pressure i.e. hypertension

  The renal artery constriction may be due to stenosis of renal artery or functional or pathological increase in resistance of the renal arteries such as due to atherosclerosis or excessive levels of vasoconstrictors.

- **Two-Kidney Goldblatt Hypertension**
  - Hypertension resulting when artery to one kidney is constricted while the artery to other kidney is normal
  - Constricted kidney release renin and retains salt and water

- The normal kidney also retains salt and water in response to renin produced by the ischemic kidney
- Consequently, hypertension develops

- **Hypertension in preeclampsia (Toxicity of pregnancy):**
  - Ischemia of placenta and subsequent release of toxic factors by placenta
  - These factors cause dysfunction of vascular endothelial cells throughout the body, including blood vessels of kidney
  - This endothelial dysfunction decreases the release of nitric oxide and other vasodilator substances causing
    1. Vasoconstriction
    2. Decreased rate of fluid filtration from glomeruli into renal tubules
    3. Impaired renal pressure natriuresis
    4. Development of hypertension

- **Acute neurogenic hypertension caused by:**
  1. Strong stimulation of sympathetic nervous system
  2. When nerves leading to baroreceptors are cut or when tractus solitarius is destroyed on each side of medulla oblongata

- **Monogenic hypertension**: Hypertension caused due to mutation of a single gene

- **Primary or essential hypertension** (90 – 95%) – hypertension of unknown origin
  Secondary hypertension – Hypertension that are secondary to known causes such as renal artery stenosis or monogenic forms of hypertension

- Cause of Primary Hypertension may be excessive weight gain and a sedentary life style. Adiposity may account for 65 – 75% of the risk for developing primary hypertension.

- Salt-sensitive hypertension may occur with different types of chronic renal disease because of gradual loss of nephrons or because of normal aging.

- Treatment of essential hypertension:
  1. Lifestyle modifications aimed at increasing physical activity and weight loss in patients
  2. Drugs:
     - Vasodilator drugs
     - Natriuretic or diuretic drugs

- Arterial pressure control mechanisms that work within seconds or minutes
  1. Baroreceptor feedback mechanism

2. CNS ischemic response
3. Chemoreceptor mechanism

- Arterial pressure control mechanisms that act after many minutes (30 minutes to several hours):
  1. Renin-Angiotensin vasoconstrictor mechanism
  2. Stress relaxation of vasculature
  3. Shift of fluid through the tissue capillary walls in and out of circulation to readjust the blood volume as needed

- Long-term mechanism for arterial pressure regulation is renal-body fluid mechanism.

- Cardiac output is the quantity of blood pumped into aorta each minute by the heart.
- Venous return is the quantity of blood flowing from the veins into the right atrium each minute.

- **Cardiac output values:**
  - In young healthy men = 5.6 L/min
  - In women = 4.9 L/min
  - Average value = 5 L/min

- **Frank – Starling Law of the heart:**
  This law states that when increased quantities of blood flow into the heart, the increased volume of blood stretches the walls of the heart chambers. As a result of the stretch, the cardiac muscle contracts with increased force, and this action ejects the extra blood that has entered from the systemic circulation.

- Stretch of the sinus node increase heart rate by 10 – 15%
  Stretched right atrium initiates Bainbridge reflex to increase heart rate

- When TPR increase, cardiac output falls
  When TPR decrease, cardiac output increase

- **Factors that cause a hyperactive heart:**
  1. Nervous stimulation
  2. Hypertrophy of heart muscle

- **Factors that cause a hypoeffective heart**
  1. Increased arterial pressure against which the heart must pump, such as in severe hypertension
  2. Inhibition of nervous excitation of heart
  3. Pathological factors that cause abnormal heart rhythm or rate of heartbeat
  4. Coronary artery blockage, causing a heart attack

5. Vulvular heart disease
6. Myocarditis, an inflammation of heart muscle
7. Cardiac hypoxia

- Conditions in which cardiac output is increased due to decreased TPR
  1. Beriberi
  2. Arteriovenous fistula (also called AV shunt)
  3. Anemia

- When cardiac output falls so low that the tissues throughout the body begin to suffer nutritional deficiency, the condition is called **cardiac shock**.

- Low cardiac output due to heart abnormalities:
  1. Severe coronary blood vessel blockage and consequent myocardial infarction
  2. Severe vulvular heart disease
  3. Myocarditis
  4. Cardiac tamponade
  5. Cardiac metabolic derangements

- Conditions of low cardiac output due to decreased venous return:
  1. Decreased blood volume e.g. due to hemorrhage
  2. Acute venous dilation
  3. Obstruction of large veins
  4. Decreased tissue mass, especially decreased skeletal muscle mass
  5. Decreased metabolic rate of the tissues e.g. hypothyroidism

- The normal external cardiac pressure is equal to the normal interpleural pressure, which is about -4mmHg

- Factors that alter external pressure on heart:
  1. Cyclical changes of interpleural pressure during respiration
  2. Breathing against a negative pressure
  3. Positive-pressure breathing
  4. Opening the thoracic cage
  5. Cardiac tamponade

- **Cardiac tamponade** – Accumulation of large quantity of fluid in pericardial cavity around the heart

- Factors that affect venous return to the heart from the systemic circulation:
  1. Right atrial pressure
  2. Mean systemic filling pressure (Psf)

3. Resistance to blood flow between peripheral vessels and the right atrium

- The greater is the volume of blood in the circulation, the greater is the mean circulatory filling pressure
  At 5000ml, the normal value of filling pressure is 7mmHg.
  At normal blood volume, maximal sympathetic stimulation increase mean circulatory filling pressure to about 14mmHg.
  Complete inhibition of sympathetic stimulation decrease mean circulatory filling pressure to about 4mmHg.

- The greater the difference between Psf and right atrial pressure, the greater becomes the venous return.
  The difference between these two pressures is called the pressure gradient for venous return.
  When pressure gradient for venous return is zero, there is no venous return

- $\mathbf{V_R} = \frac{Psf - PRA}{PVR}$

QUANTITY	NORMAL VALUES
VR : Venous Return	5 L/min
Psf : Mean systemic filling pressure	7 mmHg
PRA : Right atrial pressure	0 mmHg
PVR: Reistance to venous return	1.4 mmHg/L/min

- When right atrial pressure becomes equal to Psf, venous return becomes zero at all levels of resistance to venous return because there is no pressure gradient to cause flow of blood.

- **Effect of sympathetic stimulation on cardiac output:**
  1. Increased pumping effectiveness of heart
  2. Increased Psf
  3. Increased cardiac output
  4. No change in right atrial pressure

- **Effect of sympathetic inhibition on cardiac output:**
  1. Psf falls
  2. Effectiveness of heart as pump decreases
  3. Cardiac output falls

- **Compensatory effects initiated in response to increased blood volume:**
  1. Increased cardiac output increase the capillary pressure so that fluid begins to transude out of the capillaries into tissues, thereby returning blood volume towards normal
  2. Stress-relaxation of veins to reduce Psf

3. Increase in peripheral vascular resistance to increase the resistance to venous return

- **Effects of opening a large AV fistula**

  <u>Immediate Effects</u>
  - Increase in venous return due to large decrease in resistance to venous return
  - Slight increase in cardiac output (from 5 L/min to 13 L/min)
  - Increase in right atrial pressure (to +3 mmHg)

  <u>Effects about 1 minute later i.e. after sympathetic stimulation</u>

  - Increase in Psf from 7 to 9 mmHg
  - Elevation of cardiac output further (16 L/min)
  - Increase in right atrial pressure (4 mmHg)

  <u>Effects after several weeks</u>

  - Psf increase to +12 mmHg
  - Prolonged increased workload on heart cause heart muscle to hypertrophy slightly
  - Cardiac output increase further (20 L/min)
  - Right atrial pressure increase further (6 mmHg)

- **Fick's procedure for measuring cardiac output**

  Cardiac output (L/min) = $\frac{\text{Oxygen absorbed per min by the lungs (ml/min)}}{arteriovenous\ Oxygen\ difference\ (\frac{ml}{L} of\ blood)}$

  Cardiac output = $\frac{200}{200-160} = \frac{200}{40}$

  Cardiac output = 5 L/min

- The rate of oxygen absorption by the lungs is measured by the rate of disappearance of oxygen from the respired air, using any type of oxygen meter.

- Reduction of oxygen level in muscle tissue during exercise cause release of vasodilator substances. These vasodilators cause muscle arterioles to dilate during exercise and cause increase in blood flow to muscles. These **vasodilators** include:
  1. Adenosine
  2. Potassium ions
  3. ATP
  4. Lactic acid
  5. CO_2

- **Circulatory re-adjustments during exercise:**
  1. Sympathetic nervous system activation in many tissues with consequent stimulatory effects on circulation

2. Increase in arterial pressure
3. Increase in cardiac output

- Coronary blood supply:
  - The **left coronary artery** supplies mainly the anterior and left lateral portions of the left ventricle
  - **Right coronary artery** supplies most of the right ventricle, as well as posterior part of left ventricle in 80 – 90% of people
  - Most of the coronary venous blood flow from the left ventricular mucle returns to the right atrium of the heart by way of the **coronary sinus** which is about 75% of the total blood flow
  - Most of the coronary venous blood from the right ventricular muscle returns through small **anterior cardiac veins** that flow directly into the right atrium
  - A very small amount of coronary venous blood also flows back into heart through very minute **thebasian veins,** which empty directly into all chambers of heart.

- Epinephrine and norepinephrine can have vascular constrictor and vascular dilator effects, depending on the presence or absence of constrictor or dilator receptors in blood vessel walls.
  The constrictor receptors are called **alpha receptors.**
  The dilator receptors are called **beta receptors.**
  Both alpha and beta receptors exist in coronary vessels.

- Under resting conditions, cardiac muscle normally consumes more fatty acids than carbohydrates to supply its energy (almost 70% of energy is derived from fatty acids)

- The area of muscle that has zero flow or so little flow that it cannot sustain cardiac muscle function is said to be infarcted.

- **Causes of death after coronary occlusion:**
  1. Decreased cardiac output
  2. Damming of blood in the pulmonary blood vessels and death resulting from pulmonary edema
  3. Fibrillation of heart
  4. Rupture of heart

- Factors involved in tendency of heart to fibrillate after acute coronary occlusion:
  1. Elevated extracellular potassium concentration
  2. Injury current in the infarcted area cause electric current to flow from ischemic area of the heart to normal area and can elicit abnormal impulse, which cause fibrillation
  3. Powerful sympathetic stimulation after an infarction increases irritability of cardiac muscle and thereby predisposes to fibrillation

4. Circus movement.
   Cardiac muscle weakness caused by myocardial infarction often causes the ventricle to dilate excessively. This excessive dilation increases the pathway length for impulse conduction in the heart and frequently causes abnormal conduction pathways around the infarcted area of cardiac muscle. Both these effects predispose to the development of circus movement.

- **Drugs administered during acute angina attack:**
  1. Short-acting vasodilators i.e. nitroglycerin and other nitrate drugs
  2. Angiotensin-converting enzyme inhibitors
  3. Angiotensin receptors blockers
  4. Calcium channel blockers
  5. Ranolazine

- Beta blockers such as propranolol are used for prolonged treatment of angina pectoris

- After the first few minutes of an acute heart attack, a prolonged semichronic state begins, characterized mainly by two events:
  1. Retention of fluid by the kidneys
  2. Varying degrees of recovery of the heart over a period of weeks to months

- **Effects of fluid retention by the kidneys:**
  1. Increased blood volume increases venous return
  2. Distends the veins which reduced the venous resistance and allows even more ease of flow of blood to the heart

- **Detrimental effects of excessive fluid retention by kidneys in severe cardiac failure**:
  1. Increased workload on the damaged heart
  2. Overstretching of heart which further weakens the heart
  3. Filtration of fluid into the lungs, causing pulmonary edema and consequent deoxygenation of blood
  4. Development of extensive edema in most parts of body

- **Compensated heart failure** – an increase in right atrial pressure can maintain the cardiac output at a normal level, despite continued weakness of heart

- **Decompensated heart failure** – the state of heart failure in which the failure continues to worsen
  - Cardiac output falls
  - Fluid retention by kidneys increase
  - Right atrial pressure rises

- **Treatment of decompensated heart failure:**
  1. Strengthening the heart by administering a cardiotonic drug, such as digitalis, so that the heart becomes strong enough to pump adequate quantities of blood required to make the kidneys function normally again
  2. Administering diuretic drugs to increase kidney excretion while at the same time reducing salt and water intake, which results in a balance between fluid intake and output, despite low cardiac output.

- The most important problems of left heart failure include pulmonary vascular congestion and pulmonary edema.

- In a healthy heart, the arterial pressure usually must be reduced below about 45 mmHg before cardiac deterioration sets in.
  However, in a heart that already has a blocked major coronary vessel, deterioration begins when the coronary arterial pressure falls below 80 to 90 mmHg. In other words, even a smaller decrease in arterial pressure can now set off a vicious cycle of cardiac deterioration.
  For this reason, in treating myocardial infarction, it is extremely important to prevent even short periods of hypotension.

- **Cardiogenic shock treatment** (within one hour of cardiogenic shock)
  1. Immediate administration of digitalis
  2. Surgically removing the block in the coronary artery, often in combination with a coronary bypass graft
  3. Catheterizing the blocked coronary artery and infusing streptokinase or tissue-type plasminogen activator enzymes that cause dissolution of the clot.

- Excess potassium is one of the most powerful stimuli for aldosterone secretion, and the potassium concentration rises in response to reduced renal function in those with cardiac failure. The elevated aldosterone level further increases reabsorption of sodium from the renal tubules, which in turn leads to a secondary increase in water reabsorption

- **Reduced renal output of urine during cardiac failure has several known causes**
  1. Decreased glomerular filtration rate due to
     a. Reduced arterial pressure
     b. Intense sympathetic constriction of afferent arterioles of kidney
  2. Activation of renin-angiotensin system and increased reabsorption of water and salt by renal tubules
  3. Increased aldosterone secretion
  4. Increased ADH secretion
  5. Activation of sympathetic nervous system

- **Natriuretic peptides** are hormones released by the heart when it becomes stretched. **Atrial natriuretic peptide** (ANP) is released by atrial walls, and **brain natriuretic peptide** (BNP) is released by ventricular walls.
  These natriuretic peptides have a direct effect on kidneys to increase their excretion of salt and water greatly.

- **Measures to be taken to reverse acute pulmonary edema:**
  1. Putting tourniquets on both arms and legs to sequester much of the blood in the veins and, therefore, decrease the workload on the left side of the heart.
  2. Administering a rapidly acting diuretic, such as furosemide, to cause rapid loss of fluid from the body
  3. Giving the patient pure oxygen to breathe to reverse the blood oxygen desaturation, heart deterioration, and peripheral vasodilation.
  4. Administering a rapidly acute cardiotonic drug, such as digitalis, to strengthen to heart.

- Heart failure associated with impaired cardiac contractility is often referred to as systolic heart failure with reduced ejection fraction (**HFrEF**)

- Heart failure can also be associated with normal ejection fraction if the heart muscle become thickened and stiff (concentric hypertrophy), so that filling of ventricles is impaired, and the ventricles hold a smaller than usual volume of blood. This condition is often referred to as heart failure with preserved ejection fraction (**HFpEF**)

- High-Output Cardiac Failure caused by:
  1. Atriovenous fistula that overloads the heart because of excessive venous return, even though pumping capability of heart is not depressed
  2. Beriberi, in which the venous return is greatly increased because of diminished systemic vascular resistance but, at the same time, the pumping capability of heart is depressed.

- S_1 – closure of AV valves at beginning of systole
  S_2 – closure of semilunar valves (aortic and pulmonary) at the end of systole
  S_3 – a weak rumbling heart sound heard at the beginning of middle third of diastole

- **Duration of heart sounds:**
  S_1 = 0.14 sec
  S_2 = 0.11 sec

- S_2 has a higher frequency than S_1

- The third heart sound may be normally present in children, adolescents, and young adults but generally indicates systolic heart failure in older adults.

- Fourth heart sound is often heard in older patients with left ventricular hypertrophy

- Rheumatic fever is an autoimmune disease in which the heart valves are likely to be damaged or destroyed. The disease is usually initiated by streptococcal toxin.

- A valve in which the leaflets adhere to one another so extensively that blood cannot flow through it normally is said to be stenosed

- In patients with severe aortic stenosis, sound vibrations can often be felt with the hand on upper chest and lower neck, a phenomena known as **thrill**.

- **Heart murmurs** – Abnormal heart sounds produced when abnormalities of heart valves are present. These may be:
    - Systolic murmur of aortic stenosis
    - Diastolic murmur of aortic regurgitation
    - Systolic murmur of mitral regurgitation
    - Diastolic murmur of mitral stenosis

- In aortic stenosis and aortic regurgitation, the net stroke volume output of the heart is reduced

- Compensatory responses to aortic stenosis and aortic regurgitation:
    1. Hypertrophy of left ventricle
        a. Eccentric Hypertrophy – produced due to aortic regurgitation. Enlargement of ventricular chambers take place
        b. Concentric Hypertrophy – produced due to aortic stenosis or in circumstances where afterload of the heart is increased, such as in chronic hypertension.
        Concentric hypertrophy is associated with thickened walls and a smaller ventricular chamber. This may allow the left ventricle to develop as much as 400 mmHg of intraventricular pressure at systolic peak.
    2. Increase in blood volume

- Severe aortic valve stenosis and aortic regurgitation often causes ischemia of the heart muscle due to decreased coronary blood flow.

- Beyond a critical stage in aortic valve lesions (aortic valve stenosis and regurgitation), the left ventricle cannot keep up with the work demand. As a consequence, the left ventricle dilates and cardiac output begins to fall; blood simultaneously dams up in the left atrium and in the lungs behind the failing left ventricle. The left atrial pressure rises progressively, and at mean left atrial pressure above 25 to 40 mmHg, serious edema appears in the lungs

- Ordinarily, lethal edema does not develop until the mean left atrial pressure rises above 25 mmHg, and sometimes as high as 40 mmHg, because the lung lymphatic vesssels enlarge many times and can carry fluid rapidly away from the lung tissues.

- In late stages of mitral stenosis, atrial fibrillation often occurs

- Congenital anamolies of heart and its associated vessels:
  1. Stenosis of the channel of blood flow at some point in the heart or in a closely allied major blood vessel
  2. Left-to-right shunt thus failing of blood flow through systemic circulation
  3. Right-to-left shunt, thus failing of blood flow through lungs

- **Coarctation of the aorta** is a birth defect in which a part of the aorta is narrower than usual

- **Patent ductus arteriosus (left-to-right shunt)** is an abnormal connection between the aorta and the pulmonary artery in the heart

- **Machinery murmur** heard in patients with patent ductus arteriosus when baby grows to 1 to 3 years of age
  - A harsh blowing murmur heard in pulmonary artery area of chest
  - Sound much more intense during systole when aortic pressure is high
  - Sound much less intense during diastole when aortic pressure falls low

- **Teratology of Fallot (Right-to-left shunt)** is the most common cause of blue baby.
  In this condition, four abnormalities of heart occur simultaneously:
  1. The aorta originates from the right ventricle rather than the left, or it overrides a hole in the septum, receiving blood from both ventricles.
  2. Because the pulmonary artery is stenosed, much lower than normal amounts of blood pass from the right ventricle into the lungs; instead, most of the blood passes directly into the aorta, thus bypassing the lungs.
  3. Blood from the left ventricle flows through a ventricular septal hole into the right ventricle and then into the aorta that overrides this hole.

4. Because the right side of the heart must pump large quantities of blood against the high pressure in the aorta, its musculature is highly developed, causing an enlarged right ventricle.

- **Circulatory shock** is the 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.

- The circulatory shock that results from diminished cardiac pumping ability is called **cardiogenic shock.**

- **Hypovolemia** means diminished blood volume. Hemorrhage is the most common cause of **hypovolemic shock.**

- Circulatory system can recover as long as the degree of hemorrhage is no greater than a certain critical amount. Thus, hemorrhage beyond a certain critical level causes **progressive shock.**

- The factors that cause a person to recover from moderate degree of shock are the negative feedback control mechanisms of the circulation that attempt to return cardiac output and arterial pressure back to normal levels. These include:
  1. Baroreceptor reflexes – sympathetic stimulation
  2. CNS ischemic response – powerful sympathetic stimulation if arterial pressure falls below 50 mmHg
  3. Reverse stress-relaxation of circulatory system – causes blood vessels to contract around diminished blood volume so blood volume fills circulation more adequately
  4. Increased secretion of renin by the kidneys and formation of Angiotensin II
  5. Increased secretion of vasopressin/ ADH
  6. Increased secretion of epinephrine and norepinephrine
  7. Compensatory mechanisms that return blood volume back towards normal including:
     a. Absorption of large quantities of fluid from intestinal tract
     b. Absorption of fluid into blood capillaries from interstitial spaces of body
     c. Conservation of water and salt by the kidneys
     d. Increased thirst and appetite for salt

- **Factors leading to progressive shock:**
  1. Cardiac Depression
     When the arterial pressure falls low enough, coronary blood flow decreases below that required for adequate nutrition of the myocardium, weakening of heart muscle and decreasing the cardiac output more.

2. Vasomotor failure due to diminished blood flow to brain's vasomotor center
3. Blockage of very small vessels by sludged blood. This is due to sluggish blood flow in the microvessels and accumulation of acids (carbonic acid, lactic acid derived from tissue metabolism) in local blood vessels.
4. Increased capillary permeability causing blood to transude into the tissues, thereby decreasing blood volume.
5. Release of toxins by ischemic tissue
6. Cardiac depression caused by endotoxin
7. Generalized cellular deterioration especially liver deterioration
8. Patchy areas of tissue necrosis caused by patchy blood flows in different organs.
9. Acidosis in shock i.e. accumulation of lactic acid and carbonic acid
    - Cells carry anaerobic respiration due to poor delivery of oxygen which leads to excess lactic acid in blood
    - Poor blood flow through tissues prevent normal removal of CO_2 thus leading to carbonic acid accumulation

- Severe plasma loss can cause hypovolemic shock

- **Severe plasma loss occurs in:**
    1. Intestinal obstruction
    2. Severe burns or other denuding conditions of skin (loss of epidermis)

- **Neurogenic shock** – The shock due to increased vascular capacity so much that even normal amount of blood is incapable of filling this circulatory system adequately.
  One of the major causes of vascular capacity is loss of vasomotor tone.

- Causes of neurogenic shock:
    1. Deep general anesthesia
    2. Spinal anesthesia
    3. Brain damage

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

- **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.

- **Treatment of shock:**

SHOCK TYPE	TREATMENT
1. Shock caused by hemorrhage	Transfusion of whole blood
2. Shock caused by plasma loss	Transfusion of plasma or Dextran
3. Neurogenic and anaphylactic shock	Sympathomimetic drug such as epinephrine and norepinephrine
4. Hemorrhagic and neurogenic shock	Placing the patient with head at least 12 inches lower than the feet
5. Severe shock	Administration of glucocorticoids

- **Circulatory Arrest** – A condition in which all blood flow stops. This condition can occur as a result of cardiac arrest or ventricular fibrillation