Cardiovascular Physiology
Dr. Asma'a Khalaf

Part I

Cardiovascular system

The heart

- Heart is a muscular organ enclosed in a fibrous sac (Pericardium).
- Pericardial sac contains watery fluid that acts as a lubricant as heart moves within the sac.
- Wall of the heart is composed of cardiac muscle cells (myocardium). The inner surface of the wall is lined by a thin layer of endothelial cell;(endothelium).
- The heart is two separate pumps; a right heart which pumps blood through pulmonary artery into lungs, & a left heart which pumps blood through aorta into peripheral organ. Each of these is consists of 2 chambers, an atrium & a ventricle, separated by atrioventricular valve (left; mitral valve & right; tricuspid valve).
- Blood exists from right ventricle through pulmonary valve to pulmonary trunk, from left ventricle through aortic valve into aorta.

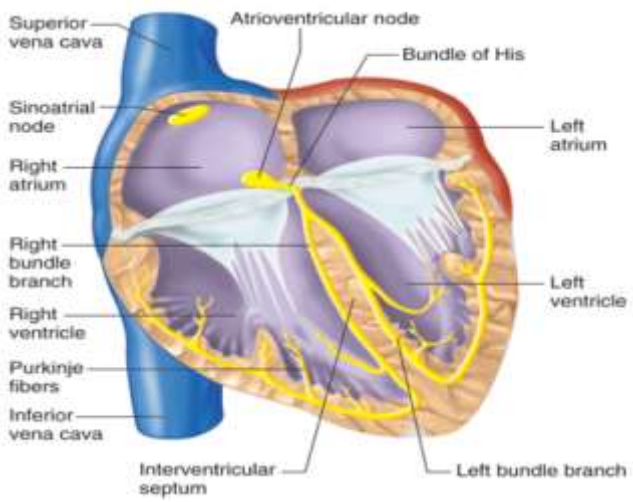
Pulmonary and Systemic Circulations

- Blood whose O2 content has become partially depleted & CO2 content has ↑ed as a result of tissue metabolism returns to right atrium, then enters ventricle, which pumps it into pulmonary arteries.
- These arteries branch to transport blood to lungs, where gas exchange occurs between capillaries & alveoli of lungs.
- O2 diffuses from air to capillary blood; while CO2 diffuses in opposite direction. Blood that returns to left atrium by pulmonary veins is therefore enriched in O2 & partially depleted of CO2. Blood that is ejected from right ventricle to lungs & back to left atrium completes one circuit: called **pulmonary circulation.**
- O2-rich blood in left atrium enters left ventricle & is pumped into a very large, elastic artery; the aorta. Aorta ascends for a short distance, makes a U-turn, then descends through thoracic & abdominal cavities. Arterial branches from aorta supply O2-rich blood to all of organ systems & are thus part of systemic circulation.
- As a result of cellular respiration, O2 concentration is lower & CO2 concentration is higher in tissues than in capillary blood. Blood that drains into systemic veins is thus partially depleted of O2 & ↑ed in CO2 content. These veins empty into two large veins; superior & inferior venae cavae that return O2-poor blood to right atrium. This completes **systemic circulation**; from heart (left ventricle), through organ systems, & back to heart (right atrium).

Physiology of Cardiac Muscle

- The heart is composed of three major types of cardiac muscle.

1- The atrial muscle.
2- The ventricular muscle.
3- Specialized excitatory & conductive muscle fibers.



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Physiological anatomy of cardiac muscle

- **Cardiac Muscle Cells (**myocytes)
- They are rectangular shaped cells connected by regions called intercalated discs. , are striated as they have typical myofibrils containing thin actin & thick myosin filaments.

- **intercalated discs** to work as a single functional organ or syncytium , contain gap junctions and desmosomes.
- **Gap junctions**, which are protein-lined tunnels, allow direct transmission of depolarizing current from cell to cell, across chambers of heart, so that cells contract in unison. Because of the way these gap junctions function, cardiac muscle cells are said to be electrically coupled.
- **desmosome** ("binding body") (Latin for *adhering spot*), is a cell structure specialized for cell-to-cell adhesion. They are one of the stronger cell-to-cell adhesion types and are found in tissue that experience intense mechanical stress, such as cardiac muscle tissue & bladder tissue.

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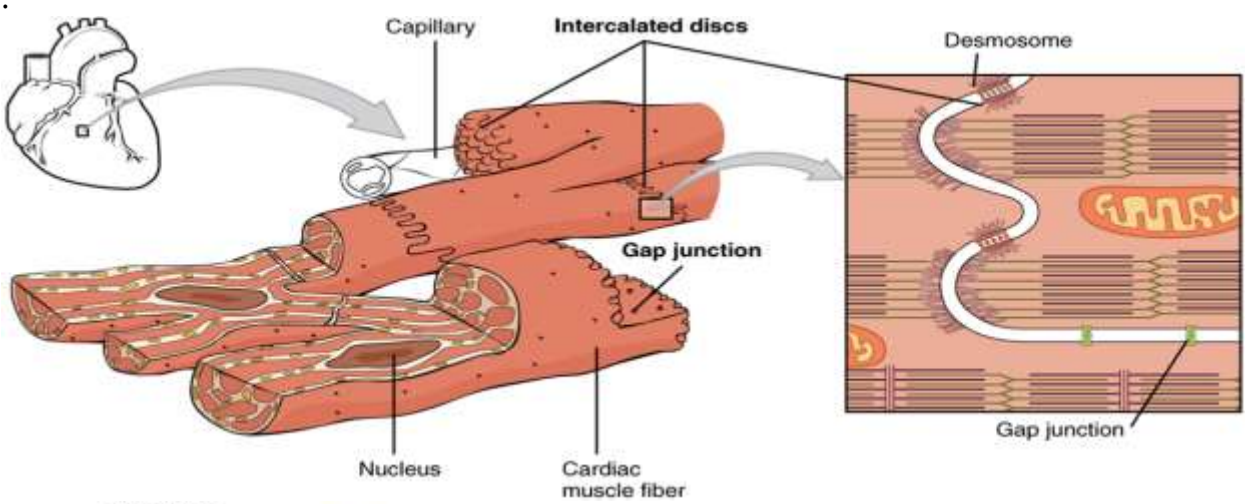
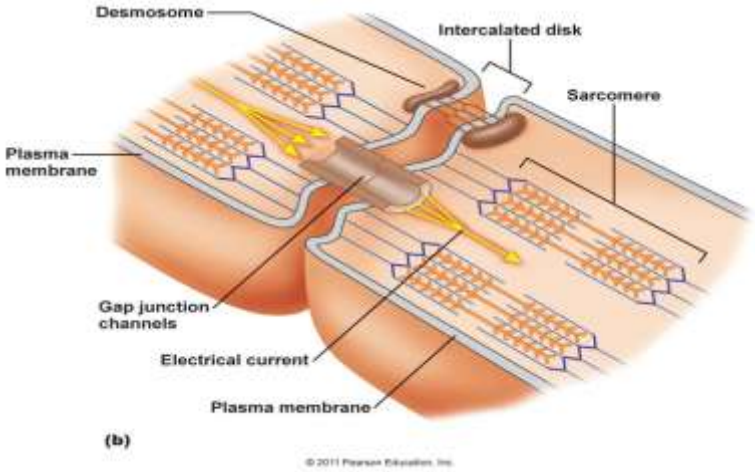


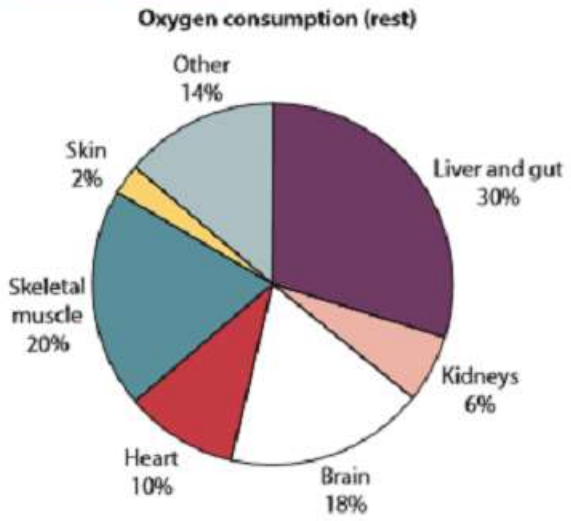


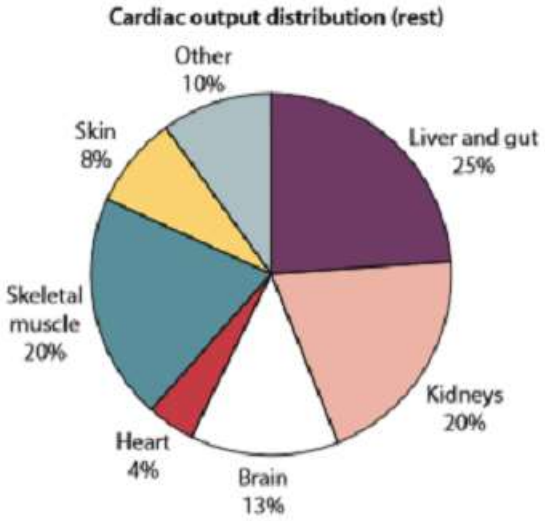
Innervations of the heart

- Heart receives a rich supply of sympathetic & parasympathetic nerve fibers.
- Parasympathetic contained in vagus nerves, release acetylcholine (Ach) which acts on muscarinic receptors.
- Sympathetic postganglionic fibers release norepinephrine (noradrenaline) which acts on beta one (β_1) adrenergic receptors distributed on cardiac muscle. Circulating epinephrine hormone from adrenal medulla also combines with the same receptors (β_1 receptors).

Blood supply of the heart

Myocardial cells receive their blood supply through arteries that branch from aorta, coronary arteries.Coronary veins drain into a single large vein, coronary sinus, which drain into right atrium.





Function of the heart valves

Function of AV valves is to prevent backflow (prevent regurgitation; leakage)of blood into atria during ventricular contraction. AV valves contain & supported by papillary muscles.

Aortic & pulmonary valves each consist of three semilunar cusps that resemble pockets projecting into lumen of aorta & pulmonary trunk. They contain no papillary muscle. Pulmonary & aortic valves allow blood to flow into arteries during ventricular contraction (systole) but prevent blood from moving in opposite direction during ventricular relaxation (diastole).

- All valves close & open passively. That is, they close when a backward pressure gradient pushes blood backward & they open when a forward pressure gradient forces blood in forward direction.
- There are no valves at entrance of superior, inferior vena cava & pulmonary veins into atria. What prevents backflow of blood from atria toward veins is compression of these veins by atrial contraction. However little blood is ejected back into veins, this represents venous pulse seen in neck veins (jugular veins) when atria contracting.

Function of papillary muscles

- AV valves (mitral & tricuspid) are supported by papillary muscles that attach to flaps of these valves by chordae tendineae.
- Papillary muscles originated from ventricular walls & contract at the same time when ventricular walls contract, but these muscles do not help valves to close or open.
- Contractions of papillary muscles prevent evertion of flaps of AV valves into atria.

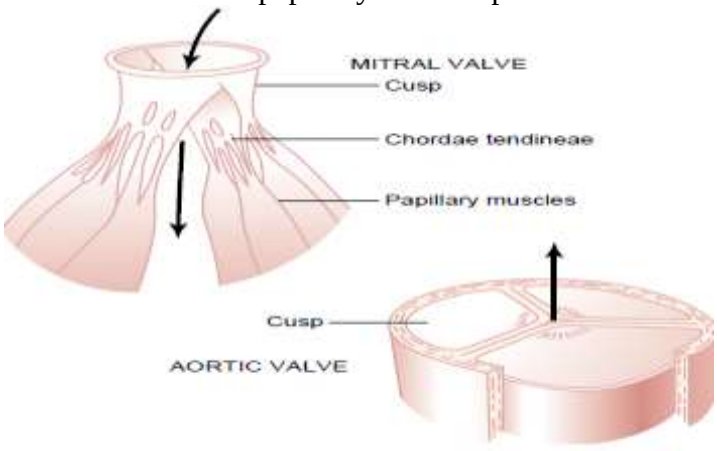


Figure 9–6
Mitral and aortic valves (the left ventricular valves).

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Properties of the cardiac muscle

- syncytium property.
- Automaticity & rhythmicity (Autorhythmicity).
- Excitability & conductivity.
- Contractility

Autorhythmicity, Excitability & conductivity:

Specialized excitatory & conductive system of the heart:

This system consists of:

1. Sinus node "SA" node (sinoatrial node), located in right atrium, concerned with generation of rhythmical impulse; it is the pacemaker of heart that initiates each heart beat.
2. Internodal pathways conduct the impulse generated in SA node to AV node.
3. AV node (atrioventricular node), located at lower end of interatrial septum, in posterior septal wall of right atrium. At which impulse from atria is delayed before passing into ventricles.
4. AV bundle (bundle of His) conducts impulse from atria into ventricles.
5. Left & right bundles of purkinje fibers, which conduct cardiac impulse to all parts of the ventricles. Purkinje fibers distribute electrical excitation to myocytes of ventricles.

The SA node as the pacemaker of the heart: (Automaticity & rhythmicity) :

- *Automaticity* is property of self-excitation (i.e. ability of spontaneously generating action potentials independent of any extrinsic stimuli).
- *Rhythmicity* is regular generation of these action potentials.
- Cardiac impulse normally arises in SA node, which has capability of originating action potential, which then spreads throughout atria, then into & throughout ventricles.
- Contractile cardiac muscle cells don't normally generate action potentials.
- All parts of conduction system are able to generate a cardiac impulse; (autorhythmicity),
    - SA node is the normal primary pacemaker.
    - AV node is a secondary pacemaker.
    - Purkinje system is a tertiary (or latent) pacemaker.
- AV node acts only if SA node is damaged or blocked, while tertiary pacemaker takes over only if impulse conduction via AV node is completely blocked.
- SA node discharges at intrinsic rhythmical rate of 100-110 times per minute (sinus rhythm).
- Under abnormal condition;
    - AV nodal fibers can exhibit rhythmical discharge a rate of 40 - 60 times/minute.
    - Purkinje fibers discharge at a rate between 15 - 40 times/minute.
- Although SA node discharges at an intrinsic rhythmical rate of 100-110 times per minute, but pulse rate 70 - 80 times/min, this is because of effect of vagal tone.
- Autorhythmicity is a myogenic property independent of cardiac innervation,as in transplanted heart (denervated heart) has no nerve supply but they beat regularly.

Self-excitation of SA node: What causes SA node to fire spontaneously?

SA node does not have a stable resting membrane potential which starts at about – 60 mV. This is due to inherent leakiness of SA nodal fibers to Na^+ ions that causes this self-excitation (Na^+ influx). in other words, because of high Na^+ ions concentration in ECF, & -ve electrical charge inside resting sinus nodal fibers, $\rightarrow Na^+$ ions outside fibers tend to leak to inside, rising membrane potential up to a threshed to fire an action potential.

Atrioventricular node (AV node):

Cardiac impulse will not travel from atria into ventricles too rapidly. There is a delay of transmission of cardiac impulse in AV node to allow time for atria to empty their blood into ventricles before ventricular contraction begins.

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Cardiac action potentials:

Action potential of SA node

Resting membrane potential of SA node is of -55 to -60 mV. The cause of this reduced - vity is that cell membrane of sinus fibers is naturally leaky to "Na^+ influx". So, Na^+ influx → a rising membrane potential "gradual depolarization" which when reaches a threshold voltage about - 40 mV→ fast Ca^{+2} & Na^+ channels opened,→ rapid entry of both Ca^{+2} & Na^+ ions causing action potential to 0 mV, to be followed by repolarization which is induced by K^+ efflux out of fiber because of opening of K^+ channels. This repolarization carries resting membrane potential down to -55 to -60 mV at termination of action potential.

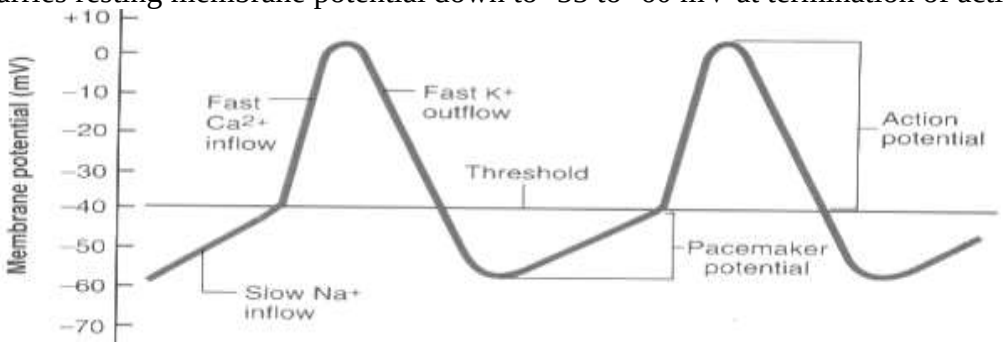


Figure: Action potentials of the SA node.

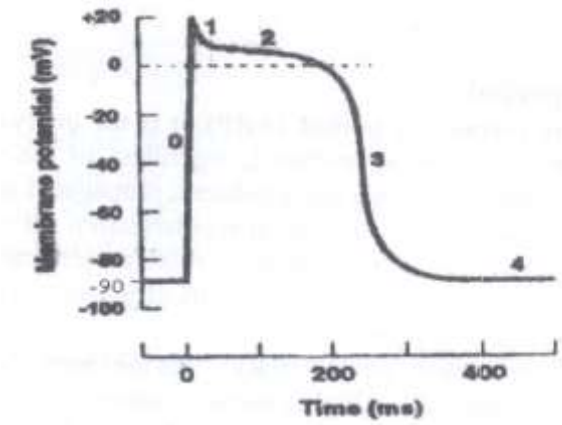
Action potential of ventricular cardiac muscle fiber

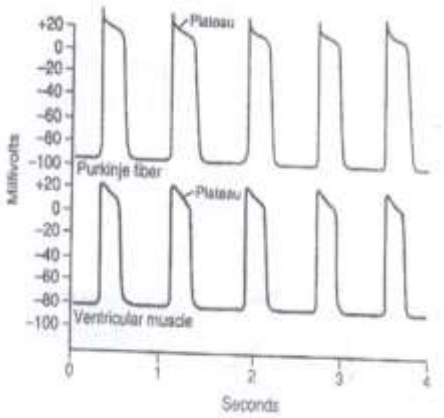
Membrane potential of cardiac ventricular muscle fiber cells is about -90 mV; interior of cell is electrically - ve in respect to exterior, due to distribution of ions mainly Na^+, K^+ & Ca^{+2} ions across its membrane.

Action potential (AP) is an electrical signal or impulse produced by ionic redistribution that potential changes into +ve inside cell (depolarization), to be followed by restoration of ions; returning back to resting potential (repolarization). Stimulation of cardiac muscle cells by SA produces a propagated AP, that is responsible for muscle contraction i.e., excitation-contraction coupling.

Ionic basis of the action potential of cardiac ventricular muscle fiber cell (phases):

- **Phase 0** (upstroke): initial rapid depolarization with an overshoot to about +20 mV are due to opening of voltage-gated Na^+ channels with rapid Na^+ influx.
- **Phase 1** (partial repolarization): initial rapid repolarization is due to K^+ efflux (K^+ outflow) followed closure of Na^+ channels when voltage reaches +20 mV.
- **Phase 2** (plateau): subsequent prolonged **plateau** is due to slower & prolonged opening of voltage-gated Ca^{+2} channels with Ca^{+2} influx, Ca^{+2} enter through these channels prolong depolarization of membrane. This plateau is **unique** for heart muscle.
- **Phase 3** (rapid repolarization): final repolarization is due to opening of voltage-gated K^+ channels at zero voltage with rapid K^+ outflow (K^+ efflux) followed closure of Ca^{+2} channels &, this restores membrane to its resting potential.
- **Phase 4** (complete repolarization): restoration of the resting potential (-90 mV) . This is achieved by Na^+-K^+ pump that works to move excess K^+ in & excess Na^+ out.





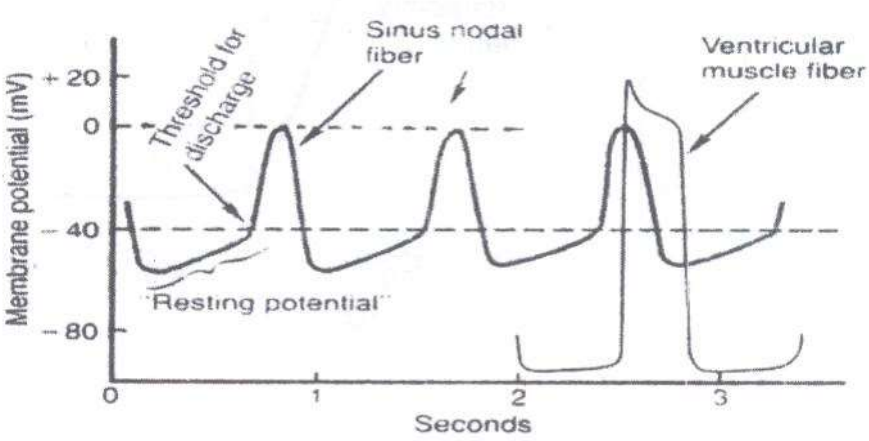
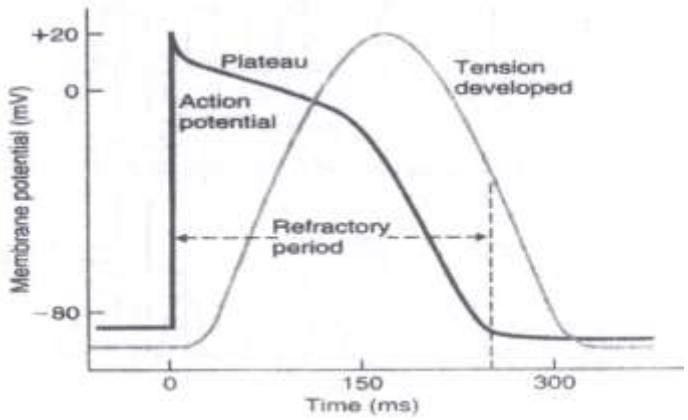


Figure: Rhythmical discharge of SA nodal fiber,compared with AP of ventricular muscle fiber.

Refractory period:

- **Absolute refractory period (ARP)**, it is the interval during which no AP can be produced, regardless of stimulus intensity. It lasts upstroke + plateau & initial repolarization till mid-repolarization at about -50 to -60 mV. It means that cardiac muscle can not be exited during whole period of systole & early part of diastole. This period prevent wave's summation & tetanus.
- **Relative refractory period (RRP)**, interval during which a 2nd AP can be produced but at higher stimulus intensity i.e., heart responds only to stronger stimuli. It lasts from end of ARP (midrepolariz.) & ends shortly before complete repolarization i.e., it lasts a short period during diastole.



Con. on Properties of cardiac muscle:

Contractility

- Ability of cardiac muscle to contract.
- Effect of various factors on contractility is called *inotropism;*
- +ve inotropic effect =↑ myocardial contractility, -ve inotropic effect =↓ contractility.

Excitation-Contraction coupling in heart muscle:

Depolarization wave reaching via T tubules causes opening of Ca^{+2} channels in sarcoplasmic reticulum(SR) adjacent to T-tubules. The ↑ed Ca^{+2} from cisternae of SR (activator Ca^{+2}; aCa^{+2}) binds to troponin C → cross bridge formation between actin & myosin, results in contraction.

In cardiac muscle, amount of this activator Ca^{+2} is often insufficient to initiate contraction, but it can be ↑ed indirectly by following mechanism:

Depolarization wave in T-tubules opens long-lasting Ca^{+2} channels in T-tubule membrane, & sarcolemma, Ca^{+2} diffuses from ECF through these channels into cardiac muscle fibre cell → a small ↑ in cytosolic (fluid of cytoplasm) Ca^{+2} concentration in T-tubules & adjacent SR. This depolarizing Ca^{+2}, although it is very small

amount, yet it is important because it acts as a signal for release of large amount of activator Ca^{+2} from cisternae of SR. Force of contraction is directly proportional to amount of cytosolic Ca^{+2}.
Relaxation results from release of actin-myosin combination, this is achieved by ↓ing intracellular Ca^{+2} to its pre- contraction level, which occur by:
1- Active re uptake of Ca^{+2} SR by Ca^{+2} pump.
2- Active pumping of excess Ca^{+2} outside fibers by Na^{+}- Ca^{+2} exchanger carrier protein (secondary active transport ; counter transport).

Heart normally cannot be stimulated again until after it has relaxed from its previous contraction because myocardial cells have long refractory periods that correspond long duration of their action potentials. Summation of contractions & tetanus are thus prevented.

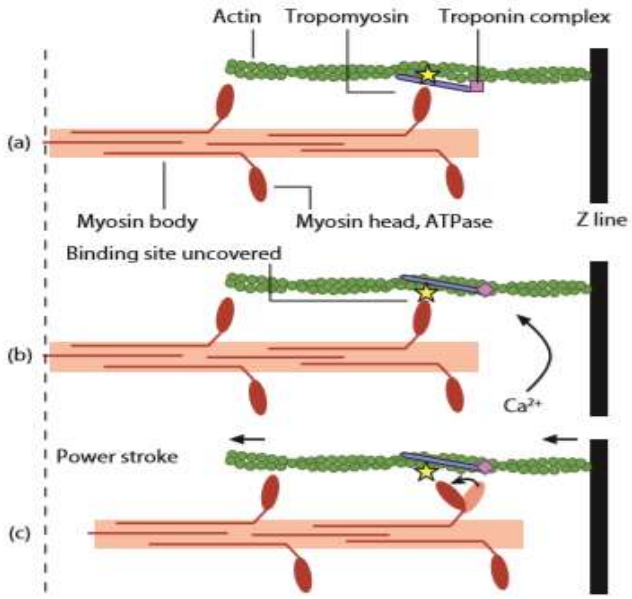


Figure 3.3 Three stages of crossbridge cycling. (**a**) Rest. The actin binding sites (yellow stars) are blocked by tropomyosin. (**b**) Ca^{2+} displaces the troponin–tropomyosin complex, exposing actin binding sites. This allows the myosin head to form a crossbridge. (**c**) Flexion of the myosin head shifts the thin filament and Z line towards the sarcomere centre. The head then disengages and reattaches further along the actin filament. The figure shows only one of many actin binding sites, four of ~400 myosin heads and one of the two heads per myosin molecule.

Factors that affect cardiac contractility:

- Mechanical
- Cardiac
- Extra cardiac

Mechanical factors:

- Preload (venous return)
- Afterload

The preload:

- It is load that determines initial length of resting muscle before contraction.
- Its is represented by end-diastolic volume (EDV) i.e., by venous return (VR).
- It affects tension developed in muscle. When venous return (EDV), ↑es, strength of ventricular contraction ↑es too →↑ in stroke volume (Frank-Starling law).

Frank-Starling's law of heart

It describes length-tension relationship in muscles; it states that force of contraction of ventricles depends on (directly proportional to) initial length of ventricular muscle fibers (i.e. to preload (VR) or EDV). This means that the greater the degree of stretching of myocardium before contraction, the greater the force of contraction. So, this law reflects relationship between ventricular EDV & stroke volume; when blood returns to heart during filling phase, this blood will distend ventricles; so ventricles will produce more powerful contraction to pump ↑ed volume of blood.

Significance of Frank-Starling's law

It allows autoregulation of myocardial contractility in following conditions:

(1) In normal hearts; the law allows changes in right ventricular output to match changes in venous return (VR), & maintains equal outputs from both ventricles.

(2) In denervated hearts (transplanted hearts); autoregulation of myocardial contractility becomes the main mechanism.

(3) In cases of rise of arterial blood pressure: stroke volume of left ventricle would ↓. However, retained blood in left ventricle + blood returning to it from left atrium during the next diastole ↑ EDV. This → a forceful contraction, thus accumulated blood in left ventricle will be ejected in spite of ↑ed arterial blood pressure.

Afterload:

It is load that muscle faces when it begins to contract. In an intact heart, afterload is produced by aortic impedance which is determined by:

- Aortic pressure (arterial systolic blood pressure).
- Arterial wall rigidity (arteriosclerosis).
- Blood viscosity (polycythemia).

Cardiac factors:

- Myocardial mass.
- Heart rate.

Myocardial mass:

A significant injury or loss of functioning ventricular muscle (e.g. due to ischemia or heart failure) ↓es the force of myocardial contractility.

Heart rate:

- Force of cardiac contractility is affected by frequency of stimulation.
- An ↑ in frequency of stimulation (i.e. shortening intervals between stimuli)→ a proportional ↑ in force of contraction.
- Accordingly, tachycardia causes a +ve inotropic effect, due to ↑ in number of depolarization (which ↑es intracellular Ca^{+2} content & its availability to troponin C).
- Bradycardia exerts a -ve inotropic action.

Extra cardiac factors:

These factors affect cardiac inotropic state & they include the following:

- Neural
- Physical
- Chemical

Neural factors:

Sympathetic stimulation & noradrenaline exert a +ve inotropic effect by;

- Increasing Cyclic-AMP in cardiac muscle fibers (which → activation of Ca^{+2} channels & more Ca^{+2} influx from ECF).
- Increasing Heart rate.

Parasympathetic stimulation & Ach exert a -ve inotropic effect (by opposite mechanism) but on atrial muscle only (vagi nerves don't supply ventricles).

Physical factors:

- A moderate rise of body temperature strengthens cardiac contractility (by ↑ing both Ca^{+2} influx & ATP formation in muscle)
- Excessive rise of body temperature (e.g. in fever) exhausts metabolic substrates in cardiac muscle & ↓es its contractility.
- Hypothermia also ↓es cardiac contractility.

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Chemical factors:

(A) Hormones:

Catecholamines (epinephrine, norepinephrine & dopamine), glucagon & thyroid hormones; all exert a +ve inotropic effect.

(B) Blood gases:

- Moderate hypoxia & hypercapnia (CO_2 excess) →↑ cardiac contractility.
- Severe hypoxia & hypercapnia directly depress cardiac muscle contractility.

(C) H^+ ion concentration (pH):

- ↑ of blood [H^+] {drop of blood pH (acidosis)} produces a -ve inotropic effect.
- ↓ of blood [H^+] { rise of blood pH (alkalosis)} produces a + ve inotropic effect.

(D) Inorganic ions:

- *Sodium*: Hypernatraemia favors Na^+ influx & Ca^{+2} efflux by Na^+-Ca^{+2} exchanger carrier, thus it has a -ve inotropic effect, & vice versa.
- *Potassium:* Hyperkalaemia has a -ve inotropic effect (weakens myocardial contractility) & may stop heart in diastole. This is because excess K^+ in ECF ↓es resting membrane potential; closer to threshold, in cardiac muscle fibers, so amplitude of AP is reduced → less influx of depolarizing Ca^{+2}. In addition, Hyperkalaemia ↑es excitation & ↓es conduction → ectopics & dilated, flaccid heart. On the other hand, hypokalaemia produces a +ve inotropic effect by an opposite mechanism.
- *Calcium:* Hypercalcaemia exerts a +ve inotropic effect as a result of more cytosolic Ca^{+2}. Whereas hypocalcaemia has a little (or no) -ve inotropic effect. However, hypocalcaemia causes cardiac flaccidity like Hyperkalaemia.

(E) *Toxins:*

Several toxins (e.g. certain snake venoms & toxin released by diphtheria) produce a-ve inotropic effect by a direct action on contractile mechanism of muscle).

(F) *Drugs:*

- Cardiac glycosides (e.g. digitalis; Digoxin): inhibit Na^+-K^+ ATPase in sarcolemma of cardiac muscle fibres, so intracellular Na^+ concentration increas↑ →↓ Na^+ influx, thus Ca^{+2} efflux through Na^+-Ca^{+2} exchanger is also ↓ed. Accordingly, intracellular Ca^{+2} ↑es, producing a +ve inotropic effect. Digitalis also ↑es slow Ca^{+2} influx during AP.
- Xanthines (e.g., caffeine & theophylline; bronchodilator); exert a +ve inotropic effect.
- Ouinidine, barbiturates, procainamide (& other anesthetic drugs) as well as Ca^{+2} blocker drugs all have a -ve inotropic effect by ↓ing Ca^{+2} influx into cardiac muscle fibres.

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The Cardiac cycle

- It is Cardiac events that occur from beginning of one heartbeat to beginning of the next.
- Each cycle is initiated by spontaneous generation of an AP in *sinus node* which travels rapidly through both atria & then through A-V bundle into ventricles.
- Because of this special arrangement of conducting system, there is a delay of > 0.1 sec. during passage of cardiac impulse from atria into ventricles. This allows atria to contract, pumping blood into ventricles before strong ventricular contraction begins. Thus, atria act as *primer pumps* for ventricles, & ventricles in turn provide major source of power for moving blood through body's vascular system.
- In a normal heart, cardiac activity is repeated in a regular cycle. At a normal heart rate of about 72 beats/min ;
  - For atria, cycle lasts about 0.15 sec. in systole & 0.65 sec. in diastole.
  - For ventricles, duration of each cardiac cycle lasts about 0.8 sec. .
  - If heart rate ↑es, diastole ↓es, means, heart beating very fast may not remain relaxed long enough to allow complete filling of ventricles before next contraction.

- For the ventricles, two major phases of cardiac cycle are:
  - Diastole; a period of ventricular relaxation in which ventricles fill with blood & it last for about 0.5 sec.
  - Systole; a period of ventricular contraction & blood ejection, lasting about 0.3 sec..

Phases of cardiac cycle:

Cardiac cycle starts by ***atrial systole followed by ventricular systole then by diastole of whole heart.***

Atrial systole (atria as a pump):

1st phase of cardiac cycle. Blood normally flows continually (passively) from veins into atria & about 75% of blood in atria flow directly into ventricles even before atrial contraction. Then, atrial contraction usually causes an additional 25% filling of ventricles. So heart can continue to operate satisfactorily under most condition without extra 25%, yet 25% is needed in exercise.

Pressure changes in atria during cardiac cycle

During atrial contraction; right atrial pressure raises 4- 6 mmHg, while left atrial pressure raises 7- 8 mmHg. In atrial pressure curve, there are 3 major pressure elevations called **a**, **c** & **v** atrial pressure waves:

- **a wave** is caused by atrial contraction.
- **c wave** is caused by bulging of tricuspid valve into right atrium during ventricular contraction because of ↑ing pressure in ventricles.
- **v wave** result from atrial filling (slow flow of blood into right atrium from veins while AV valve are closed during ventricular contraction).

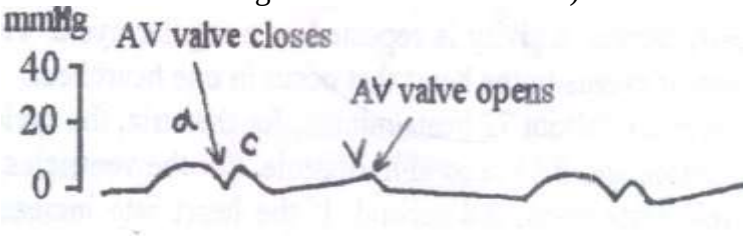

Figure: Atrial pressure curve.

Clinical importance of atrial waves

- Venous pulsations occur only in large veins near heart like jugular veins in neck (jugular venous pulsations).
- Jugular venous pulse reflects changes in right atrial pressure (central venous pressure),i.e. pressure changes within right atrium are communicated to neck jugular veins. To make jugular venous pulsations visible in neck, person has to be supine with his back at a slight angle to horizontal (45 degree). In this position, **a** & **v**

waves can be seen in jugular veins when neck is carefully examined. When venous pressure is raised as in heart failure disease, jugular veins become more prominent & pulsation can be observed in neck.

- X-descent is caused by pulling AV ring down during ventricular systole; drop in right atrial pressure.
- Y-descent is caused by opening of AV valve & escapes of blood from atrium into the ventricle; drop in right atrial pressure.

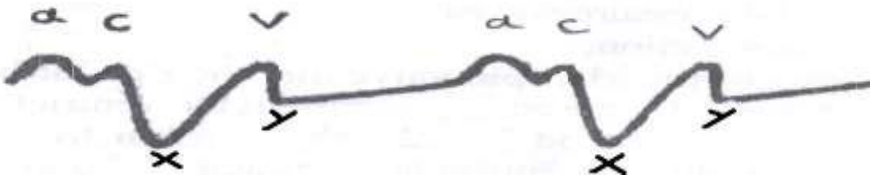

Figure: Normal jugular venous sphygmogram.

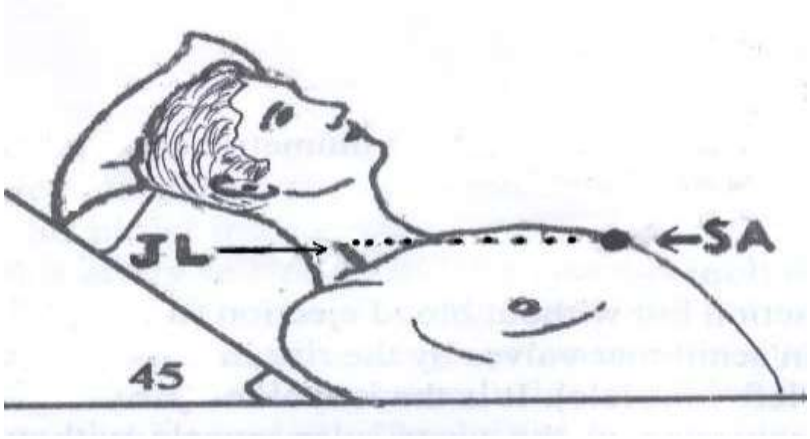

Figure: The position to examine normal jugular venous pulsation. JL = upper level where jugular pulsations appear (jugular level). SA = sternal angle level.

Ventricular cardiac cycle

It consists of three phases:

- Phase one: Ventricular filling.
- Phase two: Ventricular systole.
- Phase three: Isovolumic, isometric relaxation.

Ventricular filling

During ventricular systole, accumulated large amounts of blood in atria because of closed AV valves push AV valves open & allow blood to flow rapidly into ventricles. During atrial contraction, an additional amount of blood flows into ventricles represent 25% of filling of ventricles.

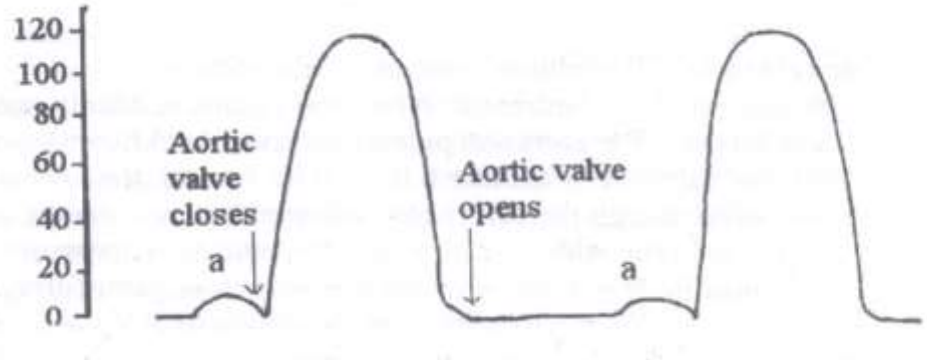

Figure: Ventricular pressure curve.

Ventricular systole:

Subdivided into two phases:

- Isovolumic, isometric contraction (isovolumetric contraction).
- Ventricular ejection.

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Isovolumetric contraction

It is ventricular contraction but without blood ejection (no emptying) just to close AV valves & to open semilunar valves by rising intraventricular pressure (from 0-80 mmHg in left ventricle). It is isovolumetric contraction, which means, only tension is ↑ing in ventricular muscle without shortening of muscle & no change in blood volume.

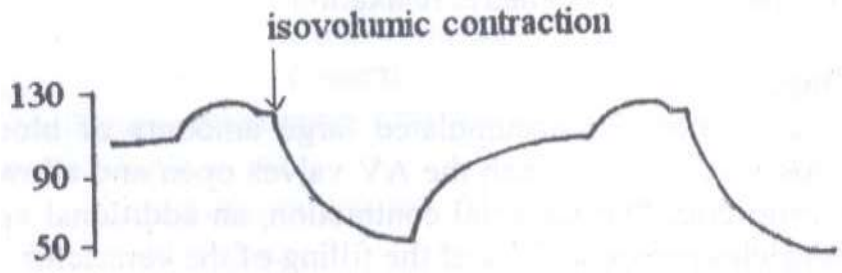

Figure: Ventricular volume curve.

Ventricular ejection

Blood ejected from ventricles into pulmonary trunk & aorta when ventricular pressure rises & forces semilunar valves open.
Left ventricular pressure rises > 80 mmHg.
Right ventricular pressure rises > 8 mmHg.

Isovolumetric relaxation:

Isovolumic, isometric relaxation; following ventricular systole, ventricular relaxation begins suddenly & ventricular pressure falls. Blood in aorta & pulmonary trunk backflows toward heart closing semilunar valves. For another 0.03-0.06 sec., ventricular muscle continues to relax, even though ventricular volume does not change giving rise to period of isovolumic relaxation in which intraventricular pressure falls rapidly back to their low diastolic levels. Meanwhile, atria have been filling with blood. When pressure exerted by blood on atrial side of AV valves exceeds that in ventricles, AV valves forced open & ventricular filling phase begins again for a new cycle of ventricular pumping.

Aortic pressure curve:

When left ventricle contracts, intraventricular pressure rises rapidly until aortic valve opens. So blood immediately flows out of ventricle into aorta, causes wall of this artery to stretch & pressure rise. Then, at the end of systole, after left ventricle stops ejecting blood & aortic valve closes, elastic recoil of arteries maintains a high pressure even during diastole (diastolic pressure = 80 mmHg).Systolic pressure inside aorta is equal to 120 mmHg. Incisura: is caused by a short period of backward flow of blood from ventricle immediately before closure of valve followed then by sudden cessation of backflow.

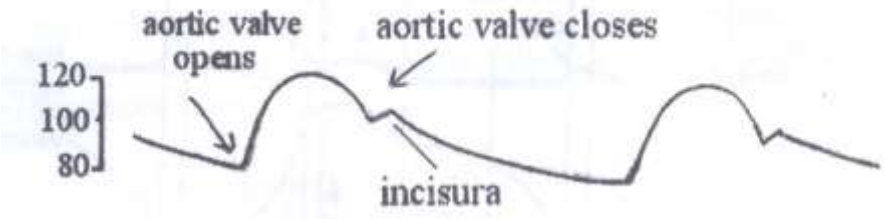

Figure: Aortic pressure curve.

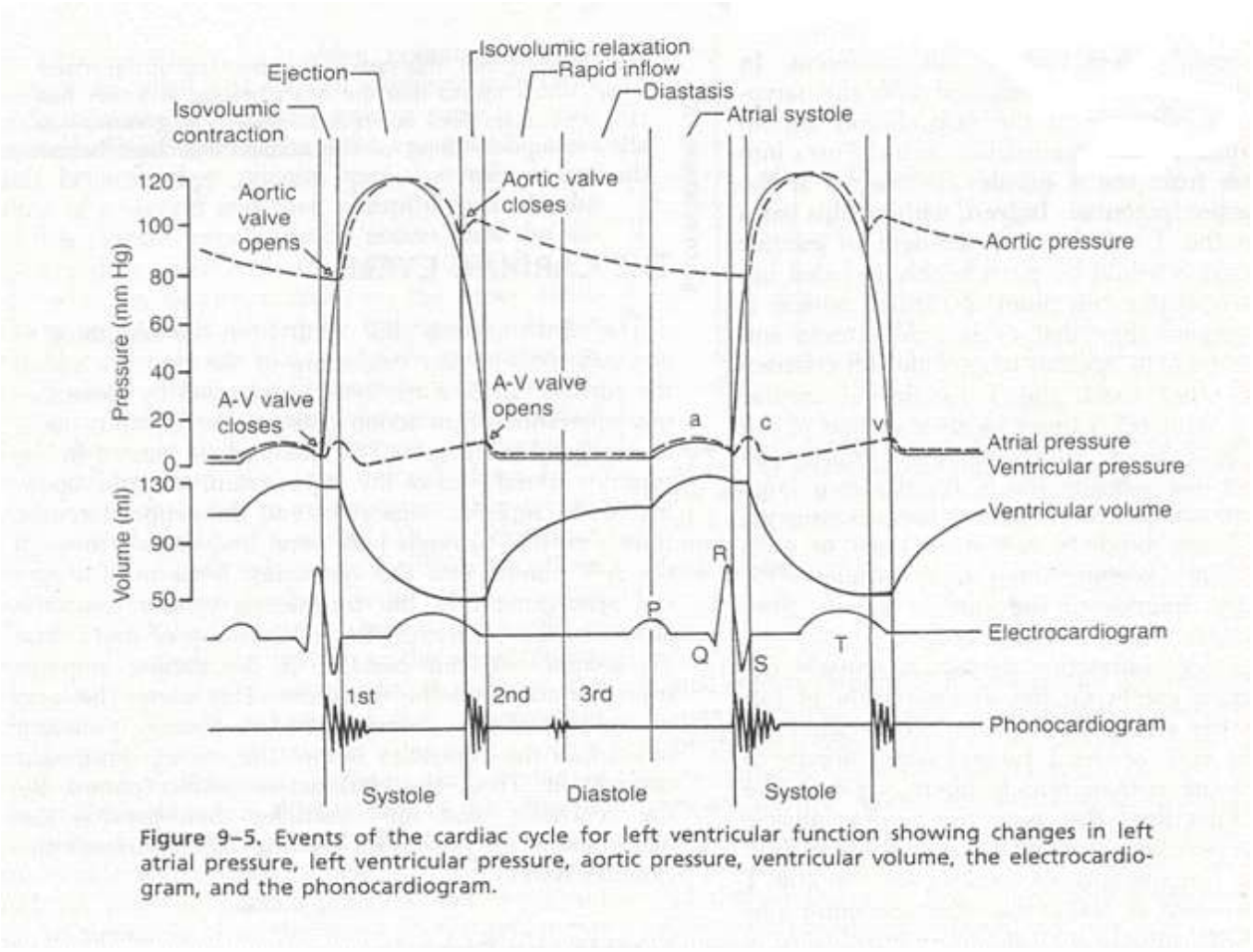

Figure 9–5. Events of the cardiac cycle for left ventricular function showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.

Cardiac output (CO)

Amount of blood pumped by each ventricle per minute, expressed in liter/minute. Normally, it is about 5 L/min. It is determined by multiplying heart rate (HR) by stroke volume (SV).

CO = HR X SV

Heart rate = number of heart beats/minute (aveage; 72 beat/min).
Stroke volume = volume of blood ejected by each ventricle with each beat.(SV is of 70 ml)
CO = 72 X 70 = 5.04 Liters.
As CVS is a closed system, CO of left ventricle = cardiac output of right ventricle i.e., the two sides of heart have same output per minute.

cardiac output= arterial blood flow = pulmonary blood flow.

- CO is a variable parameter, with level of activity of body (metabolism, exercise, age & size of body).
- It is not less than 5 L/min., at rest to supply body with O2 & to maintain normal BMR (basal metabolic rate).
- For young, healthy men, resting CO about 5.6 L/min.,for young women, this value is 10-20% less, but it is not constant.
- Heart normally cannot ↑ its CO more than 4-7 times greater than resting levels.

Control of cardiac output:

It is controlled (either ↑ed or ↓ed or maintained) by the following factors.

- Venous return (preload).
- Heart rate (HR)
- Myocardial contractility.
- Cardiac compliance.
- Afterload.

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Venous return (VR)

It is amount of blood flowing from tissues into veins & then into right or left atrium each min. (quantity of blood flowing from veins into right atrium each minute).In steady state,CO = VR because what is pumped out from left ventricle equals to what returned to right side of heart represents preload.

CO is controlled by venous return through the following mechanisms:

- Frank-Starling law; heart pumps automatically whatever amount of blood flows into right atrium from veins. This law states that when ↑ed quantities of blood flow into heart, this stretches walls of heart chambers→ cardiac muscle contracts with ↑ed force to empty expanded chambers i.e. extra blood that flows into heart (VR) is pumped without delay into aorta & flows again through circulation.
- Effect of VR on heart rate by mean of stretching heart. Stretch of SA node has a direct effect on rhythmicity of SA node itself to ↑ heart rate 10 – 15%.
- Stretched right atrium initiates a nervous reflex called ***Bainbridge reflex***, passing first to medullary vasomotor center & back to heart by symp. nerves, to ↑heart rate. (↑ HR helps to pump extra blood).

Decrease in Cardiac Output Caused by Decreased Venous Return.

Anything that interferes with VR also can →↓ed CO. Some of these factors are the following:

1. *Decreased blood volume.*
   Resulting most often from hemorrhage. Loss of blood ↓es filling of vascular system, that no enough blood in peripheral vessels to create peripheral vascular pressures high enough to push blood back to heart.
2. *Acute venous dilation.*
   In sudden acute vasodilatation, peripheral veins is especially involved (most often when sympathetic nervous system suddenly becomes inactive). Fainting often results from sudden loss of sympathetic nervous system activity, which causes peripheral vessels, (veins),to dilate markedly.This ↓es filling pressure of vascular system because blood volume can no longer create adequate pressure in flaccid peripheral blood vessels. As a result, the blood "pools" in vessels & does not return to heart.
3. *Obstruction of the large veins.*
   When large veins leading into heart become obstructed,→ cardiac output falls markedly.
4. *Decreased tissue mass, especially decreased skeletal muscle mass.*
   With normal aging or with prolonged physical inactivity→ reduction in skeletal muscle size →↓es O2 consumption & blood flow needs of muscles→↓es skeletal muscle blood flow & CO.

* Regardless of cause of low CO, if CO falls below level that is required for adequate nutrition of tissues, person is suffering from *circulatory shock (*lethal condition).

Heart rate & cardiac output:

- In resting state, (VR is constant), changes in HR 100-200 beats/min., not affect CO markedly. However,
- High heart rate (> 200 beats/min.) in patient with ventricular tachycardia (VT) or supraventricular tachycardia (SVT) may affect CO to be insufficient to maintain nutritional needs of body because :

1-↑ HR will reduces duration of ventricular diastole & so reduce time available for ventricular filling that will reduce SV.

2- Slow HR may also reduce CO, as in complete heart block disease (HR < 40 beats/min).

- In exercise, (VR is ↑ed), CO is ↑ed to meet body need by ↑ing in both HR & SV,
  - ↑ HR is through sympathetic stimulation as exercise is a stressful situation;
  - ↑ SV is through :

  a- ↑ in VR by action of skeletal muscles that squeezed & pumped blood toward heart,

  b- ↑ed myocardial contractility.

So, HR is effective in ↑ing CO if VR is ↑ed, otherwise stroke SV will be ↓ed &so ↓ed CO.

Cardiac index:

It is CO per square meter (m^2) of body surface area, as CO ↑es in proportion to surface area of body, eg., Human of 70 kg body weight has a body surface area 1.7 m^2, which means that normal cardiac index for is 3 L/min/m^2 of body surface area.

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Stroke Volume (SV)

- It is the amount of blood pumped out by each ventricle per beat.
- It is about 70 ml/beat at rest but may ↑ to 150 ml/beat with exercise.
- SV equals to amount of blood present in ventricle when systole starts just before initiation of ventricular contraction. However, ventricles don't completely empty themselves of blood during contraction (2/3 of blood is ejected, 1/3 is left there) therefore, a more forceful contraction can produce an ↑ in stroke volume.
- Stroke volume =Substruction of end-systolic volume from end-diastolic volume

SV = EDV - ESV.

EDV: ventricular blood volume at end of diastole; normally EDV = 110 - 120 ml.
ESV: ventricular blood volume at end of systole; normaly ESV = 40 ml.

* Strok volume = 70 - 80 ml.

Regulation of Stroke Volume

The stroke volume is regulated by three variables:

1. End-diastolic volume (EDV):SV is directly proportional to preload (EDV); ↑EDV →↑ SV.
2. Sympathetic nervous system input to ventricles (myocardial contractility; strength of ventricular contraction). SV is directly proportional to myocardial contractility which is influenced by cardiac sympathetic nerves (norepinephrine) & circulating epinephrine from adrenal medulla.
3. Total peripheral resistance; which is impedance to blood flow in arteries (aortic impedance). Pressure in arterial system before ventricle contracts is a function of total peripheral resistance. ↑ed arterial pressure tends to reduce SV. Total peripheral resistance presents an impedance to ejection of blood from ventricle, or an afterload imposed on ventricle after contraction. This means that SV is inversely proportional to total peripheral resistance; the greater the peripheral resistance, the lower the SV.

Ejection Fraction (EF):

It is the ratio of stroke volume to end-diastolic volume (EDV) & it reflects ventricular contractility, expressed as %, normally it averages at rest 65% (again, about 2/3 of EDV is ejected).
↑ed ventricular contractility causes ↑ in ejection fraction.
EF = SV / EDV X 100.
EF = 80/120 X 100 = 2/3 %.
In heart failure, EF is reduced; < 50%.
EF can be measured by Echocardiogram (Echo) that can measure EDV, ESV & so SV.

Myocardial contractility:

It is defined as strength of contraction at any given EDV.
Myocardial contractility exerts a major influence on SV & in turn on CO. It is reduced in heart failure.
It is measured by Ejection Fraction.
Myocardial contractility is affected by the following factors :

- Preload (i.e., EDV): controls power of cardiac contractility by Frank-Starling's law.
- Sympathetic nerve supply: resting cardiac sympathetic tone ↑es cardiac pumping power to 13-15 L/min, & maximal sympathetic stimulation (e.g. in severe muscular exercise) ↑es it to about 25 L/ min.
- Afterload (i.e., aortic impedance): ↑ in the afterload (e.g. due to rise of arterial blood pressure, aortic stenosis or polycythaemia) reduces cardiac pumping power, & vice versa.
- Ventricular hypertrophy; This may normally occur in some athletes as a result of prolonged strenuous exercises, & it can ↑ cardiac pumping power up to 35 L/ min.

Cardiac compliance:

It is stretchability, elasticity, it is change in volume per unit change in pressure = $\Delta V/\Delta P$, ↓ed compliance in which there is a myocardial stiffness, this is in disease condition which will affect CO as in cases of cadiomyopathies, & pericardial effusion.

Afterload:

It is resistance that oppose cardiac output. ↑ed afterload will reduce CO , &reduced total peripheral resistance (reduced afterload) causes high CO.

Conditions that ↓ total peripheral resistance & at the same time ↑CO to above normal include:

1. *Beriberi:* insufficient quantity of vitamin ***thiamine*** (*vitamin B1*) in diet, which causes diminished ability of tissues to use some cellular nutrients, & local tissue blood flow mechanisms in turn cause marked compensatory peripheral vasodilation. Total peripheral resistance ↓es→ Consequently, long-term levels of venous return & CO often ↑ to twice normal.
2. *Arteriovenous fistula (shun*t, AV shunt): occurs between a major artery & a major vein, in which blood flow directly from artery into vein. This greatly ↓es total peripheral resistance & , likewise, ↑es venous return & cardiac output.
3. *Hyperthyroidism.* In which metabolism of most tissues of body becomes greatly ↑ed. Oxygen usage ↑es, & vasodilator products are released from tissues. Therefore, total peripheral resistance ↓es markedly because of local tissue blood flow control reactions throughout body ; consequently, venous return &CO often ↑.
4. *Anemia.* In anemia, two peripheral effects greatly ↓ total peripheral resistance, as a consequence, CO ↑es greatly. One of these is reduced viscosity of blood, resulting from ↓ed concentration of red blood cells. The other is diminished delivery of oxygen to tissues, which causes local vasodilation.

Low cardiac output: (Abnormalities)

- Fainting: low CO → ischemia of brain; causing fall down (fainting). It is a protective mechanism to correct brain ischemia through ↑ing blood supply to brain.
- Shock: low CO that may cause hypotension, again leading to ischaemia to brain.

Methods for measuring cardiac output:

In human, CO is measured by indirect methods that do not require surgery:

- Oxygen fick method.
- The indicator dilution method.
- Echocardiography; it consists of emitting Ultrasonic waves to heart. Such echoes record ventricular movements, from which both EDV & ESV & so SV can be calculated. CO then can be measured by multipling SV X HR.

……..
ESV ➔ contractility & afterload.
EDV ➔ cardiac compliance & preload (venous return).

Heart Rate (HR)

It refers to ventricular rate of beating per min. It can be determined by counting arterial radial pulse, heart sounds (using stethoscope) or number of cycles in an ECG record /min. Normally, it averages 72 beats/min (range 60-100 beats/min) in young adult males during rest. HR > 100 beats/min is called **tachycardia** & HR < 60 beats/min is called **bradycardia**. Mechanisms that affect cardiac rate are said to have a chronotropic effect (chrono = time). Those that ↑ cardiac rate have +ve chronotropic effect (B_2 agonists (Salbutamol;Ventolin)); those that ↓ HR have -ve chronotropic effect (B blockers (Propranolol; Inderal).
HR is basically determined by strength of vagal tone, & is normally subjected to many physiological variations such as:

- It is about 120 beats/min in newly born infants (due to absence of vagal tone) then it ↓es to about 72 beats/min at age of 20 years.
- It is more in females than in males (due to less vagal tone in females).
- It is slowest in athletes (due to a stronger vagal tone than in sedentary persons).
- It sometimes shows diurnal variations (being lowest in early morning).

Regulation of heart rate:

HR is regulated (SA node discharge) by the following factors:

- Neural.
- Chemical.
- SA node activity.

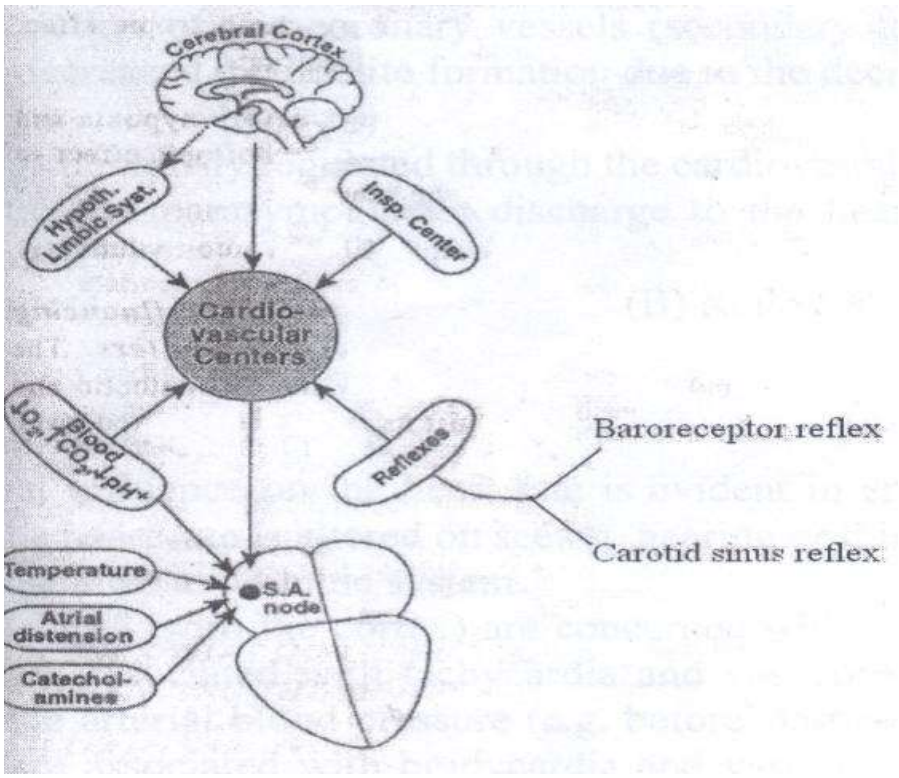

Figure: Factors that influence the heart rate.

Neural regulation of heart rate:

Heart receives both sympathetic & parasympathetic (vagal) nerves. Activity in sympathetic nerves ↑es HR, while activity in parasympathetic nerves ↓es HR.

Functions of cardiac sympathetic nerves

Sympathetic nerves supply all parts of heart (atria, ventricles, conduction system & coronary vessels). When activated, they lead to the following:

1- • ↑ HR (+ve chronotropic effect).
- ↑ in Contractility (+ve inotropic effect).
- ↑ in Excitability (causing extrasystole or paroxysmal tachycardia)
- ↑ in Conductivity (thus ↓ing AV nodal delay).

2- ↑ cardiac output.

3- Vasodilation of coronary vessels.

Functions of cardiac parasympathetic nerves

They supply atria, SA & AV nodes & coronary vessels but not ventricles. When activated, they lead to depression of all cardiac properties, resulting in:

1- • ↓ Rhythmicity i.e. HR (-ve chronotropic effect).
- ↓ Atrial contractility (-ve inotropic effect).
- ↓ Atrial excitability (terminate an attacks of atrial tachycardia or extrasystole).
- ↓ Conductivity (prolongs AV nodal delay).

2- ↓ cardiac output.

3- Vasoconstriction of coronary vessels.

Heart is nervously regulated through CV centers which control sympathetic & parasympathetic discharge to heart. The activity of these centers is affected by:

a- Reflexes. b - Higher center.

Higher centers:

(1) Cerebral cortex. Cortical influence on heart rate is evident in emotions (HR is altered on seeing, hearing or thinking of a certain event).

(2) Hypothalamus & limbic system. These structures (with cortex) are concerned with emotional reactions.

- Most emotions are associated with tachycardia & vasoconstriction which ↑es arterial blood pressure, (e.g. before examination).
- Some are associated with bradycardia & vasodilation which ↓ es arterial Blood pressure (e.g. when hearing shocking news).

(3) Respiratory center.

- Respiratory sinus arrhythmia;is ↑ HR during inspiration & ↓ HR during expiration that occurs normally in young subjects & children.
- Tachycardia occurs during inspiration is due to; excitation of vasoconstrictor center by inspiratory center, & Bainbridge reflex.

Reflexes:

Bainbridge reflex (atrial stretch reflex)

An ↑ in right atrial pressure or ↑ed distention of right atrium → heart acceleration

Baroreceptor reflex

- It is initiated by stretch receptors, located in carotid sinus & aortic arch(stretching → stimulation).
- Signals from carotid arteries transmitted through glossopharyngeal nerves, while signals from arch of aorta transmitted through vagus nerve, into CV centers.

Baroreceptor signals inhibit VCC & excite vagal center (CIC) resulting in vasodilation, ↓ed HR.

Carotid sinus reflex

- An external pressure on carotid sinus area (behind angle of mandible) produces reflex slowing of HR & peripheral vasodilation.
- The applied external pressure stimulate baroreceptors in carotid sinus which →reflex ↑ in vagal tone to heart (bradycardia) & ↓ in sympathetic vasoconstrictor tone (vasodilation).
- So an attack of paroxysmal atrial (but not ventricular) tachycardia can be terminated by initiating a carotid sinus reflex, through external massaging of carotid sinus. A strong blow on the carotid sinus area could lead to complete cardiac arrest. Some individuals pathologically have an abnormal hypersensitivity of the carotid sinus. Thus, mild pressure on carotid sinus area e.g. during shaving, produces bradycardia & generalized vasodilation, . Treatment by anticholinergic drugs (Atropine) to block vagal discharge to the heart.

Chemical regulation of heart rate:

A- Effect of changes in blood gases.

- Hypoxia.
- Hypercapnia and acidosis.

Hypoxia:

Moderate hypoxia (O_2 lack) increases heart rate by 3 mechanisms:

- Direct mechanism (by stimulating SA node pacemaker cells).
- Central mechanism (by inhibiting CIC).
- Reflex mechanism (by stimulating VCC through exciting peripheral chemoreceptors in carotid & aortic bodies.

Severe hypoxia causes reduction of HR due to inhibition of SA node activity & paralysis of medullary cardiovascular centers.

Hypercapnia & acidosis:

A moderate hypercapnia (CO_2 excess) & acidosis →↑HR by the following mechanisms:

- Inhibition of CIC.
- Stimulation of VCC through exciting peripheral chemoreceptors.
- Stimulation of VCC through exciting central chemoreceptors.

Severe hypercapnia or acidosis ↓es HR due to inhibition of SA node activity and paralysis of medullary cardiovascular centers.

B- Effects of hormones, drugs & chemicals:

- Adrenaline; Small doses ↑ HR by a direct action on (*β1)* receptors in SA node.
- Thyroxine: ↑es HR by direct stimulation of SA node & ↑ its sensitivity to catecholamines.
- Atropine: accelerates heart by blocking parasympathetic activity.
- Histamine: a potent vasodilator substance which → marked drop of arterial Blood pressure, resulting in heart acceleration.
- Bile salts: inhibit SA node activity & stimulate CIC → bradycardia.
- Autonomic drugs: Sympathomimetic drugs (amphetamine) cause tachycardia while parasympathomimetic drugs (acetylcholine) cause bradycardia.

SA node activity:

Factors that directly affect SA node activity:

- Body temperature; (physical factors) ↑ body temperature by 1 °C →↑ HR by 10-20 beats/min and vice versa.
- Mechanical factors; Right atrial distension may directly excite SA node leads to tachycardia.
- Chemical factors; The SA node is directly excited by mild hypoxia, Catecholamines, thyroxine, while it is directly inhibited by severe hypoxia and hypercapnia, bile salts, and cholinergic drugs.
- Thyroid hormones (T_3, T_4) again have direct action on SA node. Increases in the level of circulating thyroid hormones increases the rate at which SA node beats e.g., in case of Thyroitoxicosis disease, there is an increase in heart rate, (resting tachycardia; HR > 100 beats/minute).

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Arterial blood pressure (BP)

- It is pressure exerted by blood on arterial walls. Normally it fluctuates during cardiac cycle between a maximum called **systolic blood pressure (SBP**) & a minimum called **diastolic blood pressure (DBP).**
- SBP averages 120 mmHg in young adult males (range 90 -140 mmHg), & is produced by ejection of blood into aorta during left ventricular systole (>140 mmHg represents systolic hypertension).
- DBP averages 80 mmHg (range 60 - 90 mmHg), & is produced as a result of elastic recoil of aorta during ventricular diastole (> 90 mmHg represents diastolic hypertension).
- Arterial blood pressure (ABP) is systolic over diastolic pressure (e.g. 120/80). BP value less than normal lower limit called hypotension (e.g. SBP < 90 mmHg).

Pulse pressure: difference between systolic & diastolic BP & it normally averages 40 mmHg.
Pulse pressure = SBP – DBP =120 – 80 = 40 mmHg.

Mean arterial blood pressure:
Mean BP = DBP + 1/3 pulse pressure = 80 + 13 = 93 mmHg.

Functions of arterial blood pressure:

1- It maintains tissue perfusion (i.e. blood flow) throughout various tissues, including those lying above heart level (in spite of force of gravity).
2- It produces capillary hydrostatic pressure, which is concerned with formation of interstitial fluid).

Functions of Diastolic blood pressure:

a- It maintains blood flow to tissues during ventricular diastole (so, blood flow to tissues becomes continuous, not intermittent).
b- It is essential for normal coronary blood flow.
c- It prevents blood stasis in arteries during ventricular diastole.

Physiological factors that affect arterial blood pressure:

- Age: ABP is very low at birth (70-80/40-50 mmHg) then it rises progressively till about 120/80 mmHg at age of 20 years. Its rise continues gradually after that age, but its rate ↑ markedly after age of 40 years due to normal gradual loss of arterial elasticity, so it becomes normally I50/90 mmHg after age of 60years.
- Sex: ABP is slightly higher in adult ♂ than in ♀. However, it becomes slightly higher in ♀ after menopause.
- Body region: ABP is normally higher in lower limbs than in upper limbs.
- Body built: ABP is usually high in obese persons.
- Race: ABP is often high in western countries (probably due to genetic factors, but stress, environmental or dietary factors may also contribute).
- Diurnal variation: ABP is normally lowest in early morning & highest in afternoon.
- Meals: ABP ↑ slightly after meals (especially SBP) due to vasodilatation (VD) in splanchnic area, which ↑ both VR & CO.
- Exercise: ABP markedly ↑ during exercise, especially SBP (DBP not changed or even ↓).
- Emotions: ABP ↑ in most emotions especially SBP (due to ↑ed sympathetic stimulation).
- Intercourse: SBP often ↑ during intercourse.
- Sleep: ABP is slightly ↓ during sleep(due to ↓ sympathetic activity)& ↑ during nightmares.
- Environmental temperature: In hot environment, SBP ↑ slightly due to tachycardia, but DBP often↓ due to cutaneous vasodilatation. While, exposure to cold →↑SBP & DBP due to cutaneous vasoconstriction.
- Gravity: On standing, force of gravity ↑ mean ABP & venous pressure below a reference point in heart (in right atriurn) & ↓ them above that point by 0.77 mmHg.
- Respiration: ABP shows rhythmic fluctuations during respiratory cycle. It is ↓ed during inspiration because lung vascular capacity is ↑ed →↓ pulmonary VR→↓ both left ventricular CO & ABP. It is then ↑ed during expiration due to squeeze of pulmonary vascular bed → ↑pulmonary VR & left ventricular CO.