Case 2: Flow of the Heart

Block 4 Module 2

CARDIAC CYCLE

- Are the events that occur from the beginning of one heartbeat to the beginning of the next.
- It consists of a period of relaxation called diastole, during which the heart fills with blood, followed by a period of contraction called systole.

PHASES OF THE CARDIAC CYCLE

1. Atrial Systole	• Is preceded by the P wave • Contributes to, but is not essential for ventricular filling. • The increase in atrial pressure (venous pressure) caused by atrial systole is the A wave in venous pulse. • Filling the ventricle by atrial systole causes the fourth heart sound (S4), which is not audible in normal adults.
2. Isovolumetric Ventricular Contraction	• Begins after the onset of the QRS wave • When ventricular pressure becomes greater than atrial pressure, the atrio-ventricular valves (tricuspid and mitral valves) close ○ Their closure corresponds to the first heart sound (S1). • Because the mitral valve close before the tricuspid valve, the first heart sound may be split. • Ventricular pressure rises isovolumetrically as a result of contraction, but no blood leaves the ventricle because the aortic valve is closed.
3. Rapid Ventricular Ejection	• Ventricular pressure reaches its maximum value. • When ventricular pressure becomes greater than aortic. pressure, the aortic valve opens. • There is rapid ejection of blood into the aorta due to the pressure gradient between the ventricle and the aorta. • Ventricular volume decreases dramatically since most of the stroke volume is ejected during this phase. • Atrial filling begins. • The onset of the T wave marks the end of the contraction and the end of rapid ventricular ejection
4. Reduced Ventricular Ejection	• Ejection of blood from the ventricle continues but is slower. • Ventricular pressure begins to fall. • Aortic pressure also falls because run-off of blood from large arteries into smaller arteries is faster than the flow of blood from the ventricle into the aorta. • Atrial filling continues.
5. Isovolumetric Ventricular Relaxation	• Repolarization of the ventricle is complete (the T wave) • The aortic valve closes, followed by closure of the pulmonic valve; • Closure of the semilunar valves (aortic and pulmonic valves) corresponds to the second heart sound (S2). ○ Inspiration causes splitting of S2. • The atrio-ventricular (AV) valves remain closed. • Ventricular pressure falls rapidly since the ventricle is now relaxed, and ventricular volume is constant because all valves are closed. • The "blip" in the aortic pressure tracing occurs following closure of the aortic valve and is called the dicrotic notch, or incisura.
6. Rapid Ventricular Filling	• When ventricular pressure falls below atrial pressure the mitral valve opens and the left ventricle begins to fill. • Aortic pressure continues to fall because blood continues to run off into the smaller arteries. • Rapid flow of blood from the atria into the ventricles cause the third heart sound (S3), which is normal in children but in adults are associated with disease.
7. Reduced Ventricular Filling (Diastasis)	• Ventricular filling continues but at a slower rate. • The time for diastasis depends upon heart rate; ○ Increased heart rate decreases the time for ventricular filling.

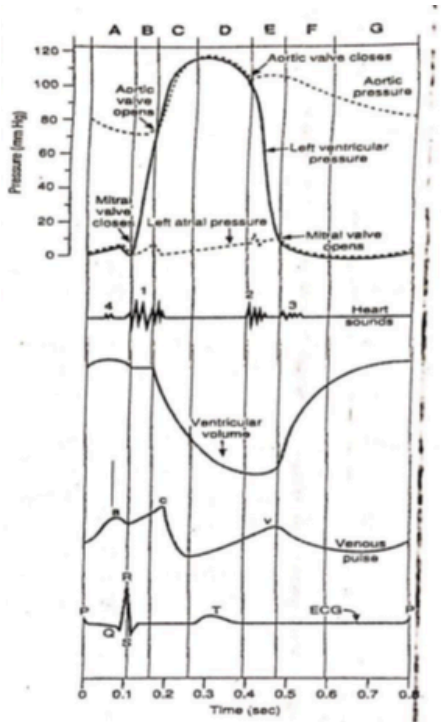


Figure 3 –12. The cardiac cycle. *A* = atrial systole; *B* = isovolumetric ventricular contraction; *C* = rapid ventricular filling; *D* = reduced ventricular ejection; *E* = isovolumetric ventricular relaxation; *F* = rapid ventricular filling; *G* = reduced ventricular filling.

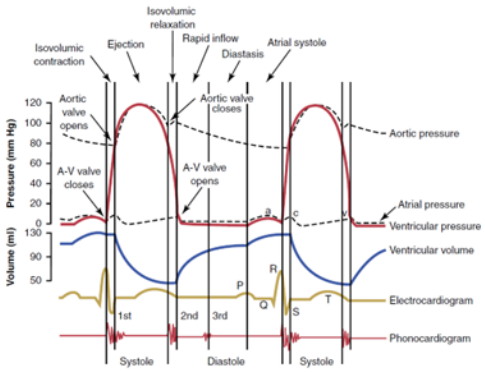


Figure 9-8. Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram. A-V, Atrioventricular.

MECHANISM OF THE ATRIAL PRESSURE CHANGES AND THE JUGULAR PRESSURE

- Atrial pressure rises during atrial systole and continues to rise during isovolumetric ventricular contraction when the AV valves are pulled down by the contracting ventricular muscle, pressure falls rapidly and then rises as blood flows into the atria until the AV valves open early in diastole.
- The return of the AV valves to their relaxed position also contributes to this pressure by reducing atrial capacity.
- Atrial pressure changes are transmitted to the great veins, producing three characteristic waves in the record of jugular pressure:

1. A wave	• Due to atrial systole. • Some blood regurgitates into the great veins when the atria contract, even though the orifices of the great veins are constricted. • In addition, venous inflow stops, and the resultant rise in venous pressure contributes to the a wave
2. C wave	• Is the transmitted manifestation of the rise in atrial pressure produced by bulging the tricuspid valve into the atria during isovolumetric ventricular contraction.
3. V wave	• Mirrors the rise in atrial pressure before the tricuspid valve opens during diastole.

HEART SOUNDS

1. First heart sound (S1)	• Is a low slightly prolonged "lub", caused by vibration set up by the sudden closure of the mitral and tricuspid valve at the start of ventricular systole. • Normally heard over the entire precordium • S1 is usually louder than S2 at the cardiac apex (left 5th ICS near the midclavicular line) • It is usually fainter than S2 at the base of the heart • It marks the beginning of ventricular systole
2. Second heart sound (S2)	• Is a shorter, high-pitched "dup", caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole. • The aortic valve component (A2) precedes the pulmonic component (P2). • S2 best heard in the medial end of 2nd right ICS while P2 is best heard in the medial end of 2nd left ICS • It is usually louder than S1 at the base of the heart
3. Third heart sound (S3)	• Soft, low-pitched heart about one-third of the way through diastole in many normal young individuals. • It coincides with the period of rapid ventricular filling and is probably due to vibrations set up by the in rush of blood.
4. Fourth heart sound (S4)	• Sometimes heard immediately before (S1) when atrial pressure is high. • It is due to ventricular filling and is rarely heard in normal adults.

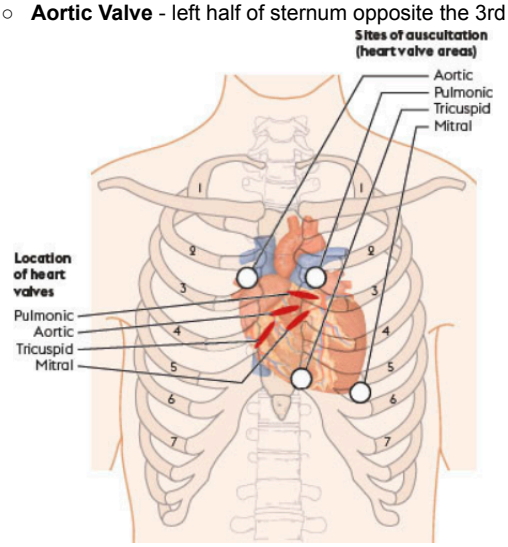
LOCATION OF VALVE AREAS

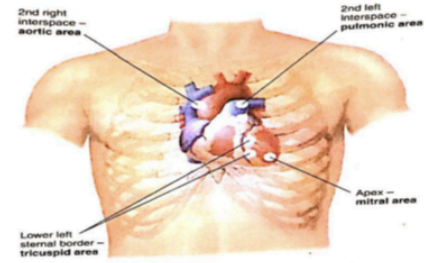
CLINICAL VALVE AREAS

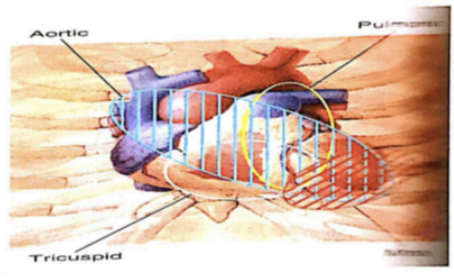
- Clinical valve areas - areas where the different heart sounds are best heard.
  - **Mitral Area** - at and around the cardiac apex (over the apex of the left ventricles)
  - **Tricuspid Area** - at or near the lower left sternal border (over the right ventricle)
  - **Pulmonic Area** - 2nd and 3rd left interspaces close to the sternum (upward along the pulmonary areas
  - **Aortic Area** - 2nd right interspace (upward along the aorta)

CLINICAL VALVE AREAS

- lies behind:
  - **Tricuspid Valve** - right half of sternum opposite the 4th ICS
  - **Mitral Valve** - left half of the sternum opposite 4th Left Costal Cartilage
  - **Pulmonary Valve** - medial end of 3rd Left Costal Cartilage and adjoining part of sternum
  - **Aortic Valve** - left half of sternum opposite the 3rd ICS.







TERMS

- **End-Diastolic Volume**
  - Increase in volume of each ventricle to about 110-120 milliliters as a result of ventricular filling during diastole
- **End-Systolic Volume**
  - The remaining volume in each ventricle at the end of systole about 40-50ml
- **Stroke Volume**
  - The amount of blood pumped out of each ventricle per beat, which is about 70ml. In a resting man of average size in supine position.
- **Preload**
  - The degree of tension on the cardiac muscle when it begins to contract or the degree to which the myocardium is stretched before it contracts.
- **Afterload**
  - AKA "the resistance against which blood is expelled"
  - Load against which the cardiac muscle exerts its contractile force
- **Ejection Fraction**
  - The fraction of the end-diastolic volume that is ejected, with each stroke, which is equal to 60%.
  - It is a valuable index of ventricular function.
- **Cardiac Output**
  - The amount of blood pumped into the aorta each minute by the heart.
- **Cardiac Index**
  - The cardiac output per minute per square meter of body surface area (average 3.26)
- **Cardiac Reserve**
  - The maximum percentage that the cardiac output can increase above the normal level.
- **Cardiac Contractility**
  - The ability of the cardiac muscle to develop force at a given muscle length.
  - Is also called inotropism
  - Can be estimated by the ejection fraction (stroke volume / end- diastolic volume), which is normally 0.55 (55%).
  - The force of contraction of cardiac muscle is dependent upon its preloading and its afterloading.
  - Agents that produce a decrease in contractility have a negative inotropic

NORMAL CARDIAC OUTPUT AND REGULATION MECHANISM

- Cardiac output is the output of the heart per unit time.
- In a resting, supine man, it averages about 5.0L/min. (70ml X 72 beats/min.).
- Variations in cardiac output can be produced by changes in cardiac rate or stroke volume.
  - The cardiac rate is controlled primarily by the cardiac innervation, sympathetic stimulation increasing the rate and parasympathetic stimulation decreasing it.
  - The stroke volume is also determined in part by neural input, sympathetic stimuli making the myocardial muscle fibers contract with greater strength at any given length and parasympathetic stimuli having the opposite effect.
- The cardiac accelerator action of the catecholamines liberated by sympathetic stimulation is referred to as their chronotropic action, whereas their effect on the strength of cardiac contraction is called their inotropic action.

EFFECTS OF VARIOUS CONDITIONS ON CARDIAC OUTPUT

EFFECT	CONDITIONS
No change	• Sleep • Moderate changes in environmental temperature
Increase	• Anxiety and excitement (50-100%) • Eating (30%) • Exercise (700%) • High environmental temperature • Pregnancy • Epinephrine
Decrease	• Sitting or standing from lying position (20-30%) • Rapid arrhythmias • Heart disease

PRESSURE VOLUME RELATIONSHIPS IN BOTH THE LEFT AND RIGHT VENTRICLE

- The movements of the right and left ventricle in ejecting the blood:
  - Ventricular pressure - Volume loops
    - Are constructed by combining systolic and diastolic pressure curves.
    - The diastolic pressure curve is the relationship between the diastolic pressure and diastolic volume in the ventricle.
    - The systolic pressure curve is the corresponding relationship between systolic pressure and systolic volume in the ventricle.
    - A cycle of ventricular contraction, ejection, relaxation, and refilling can be visualized by combining the two curves into a pressure volume loop.

A. 1➞2 (Isovolumetric or Isovolumic, or Isometric Contraction)	• Begin during diastole at point 1. • The ventricle has been filled and its volume is about 140ml (end-diastolic volume). • The pressure is low because the ventricular muscle is relaxed. • Upon excitation, the ventricle contracts and ventricular pressure increases. • Because all valves are closed, no blood can be ejected from the ventricle (isovolumetric).
B. 2➞3 (Ventricular Ejection)	• The aortic valve opens at point 2 when pressure in the ventricle exceeds pressure in the aorta. • Blood is ejected into the aorta, and the ventricular volume falls. • The volume that is ejected is the stroke volume. Thus, stroke volume can be measured graphically by the width of the pressure-volume loop.
C. 3➞4 (Isovolumetric Relaxation)	• At point 3, the ventricle relaxes. • When the ventricular pressure falls to a value less than aortic pressure, the aortic valve closes. • Because all valves are closed again, ventricular volume is constant (isovolumetric).
D. 4➞1 (Ventricular Filling)	• Once ventricular pressure falls below atrial pressure, the mitral valve opens, and filling of the ventricle begins. • During this phase, ventricular volume is increased back to about 140ml (end-diastolic volume).

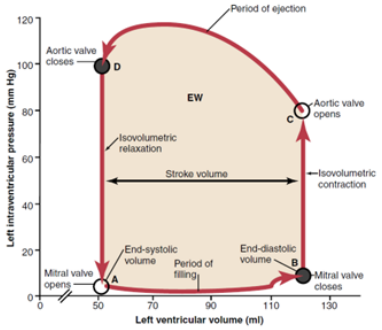


Figure 9-11. The volume-pressure diagram demonstrating changes in intraventricular volume and pressure during a single cardiac cycle (*red line*). The *shaded area* represents the net external work (EW) output by the left ventricle during the cardiac cycle.

FACTOR CONTROLLING CARDIAC OUTPUT

- **Cardiac Rate**
  - Is controlled primarily by cardiac innervation; sympathetic stimulation increases the rate and parasympathetic stimulation decreases it.
  - A heart beating at a very fast rate sometimes does not remain relaxed long enough to allow complete filling of the cardiac chambers before the next contraction. So, increase heart rate decreases cardiac output.
- **Stroke Volume**
  - Is determined in part by neural input, sympathetic stimuli making the myocardial muscle fibers contract with greater strength at any given length and parasympathetic stimuli having the opposite effect.
  - By both increasing the end-diastolic volume and decreasing the end-systolic volume, the stroke volume can be increased to as much as double the normal. So, increase stroke volume = ↑ cardiac output.

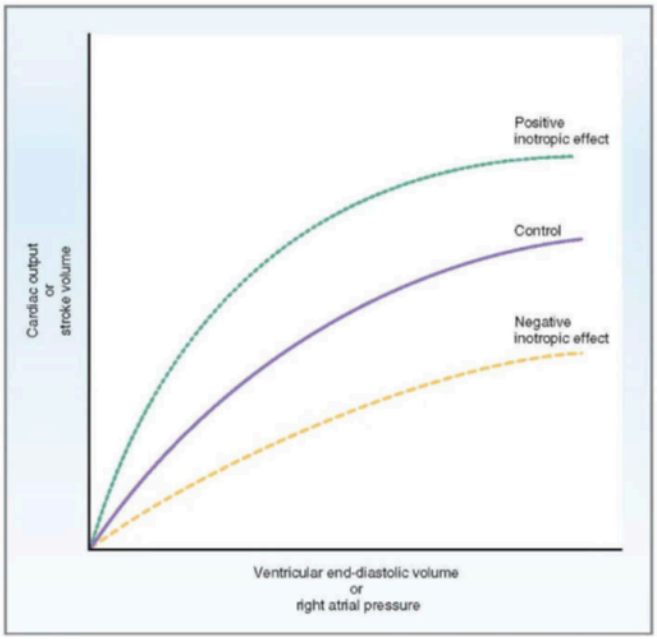
MECHANISMS OF REGULATION OF HEART PUMPING

- The basic means by which the volume pumped by the heart is regulated are:
  - Control of heart rate and strength of heart pumping by the autonomic nervous system.
  - Intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart (Frank-Starling mechanism)

MECHANISMS IN CARDIAC INTRINSIC REGULATION

FRANK-STARLING LAW

- States that the greater the heart muscle is stretched during filling, the greater the force of contraction and the greater the quantity of blood pump into the aorta.
- Describes the increase in cardiac output (or stroke volume) that occurs in response to an increase in venous pressure or end-diastolic volume
- Based on the length-tension relationship; an increase in end-diastolic volume cause an increase in fiber length, which cause an increase in developed tension.
- Is the mechanism that matches cardiac output to venous return.
- Changes in contractility shift the Frank-Starling curve upward (increased contractility) or downward (decreased contractility)
  - Increase in contractility cause an increase in cardiac output for any level of venous pressure, right atrial pressure, or end-diastolic volume
  - Decrease in contractility cause a decrease in cardiac output for any level of venous pressure, right atrial pressure, or end-diastolic volume.



LENGTH-TENSION RELATIONSHIP

- Describes the effect of ventricular cell length on the strength of contraction
- Is similar to that in skeletal muscle.

1. Preload for ventricular muscle	• Is equivalent to end-diastolic volume or venous filling pressure. • When ventricular filling is increased, the ventricular muscle fibers are stretched
2. Afterload	• Is equivalent to aortic pressure • Is increased by increasing aortic pressure
3. Sarcomere length	• Determine the maximum number of cross-bridges that can form • Determine maximum tension or strength of contraction
4. Velocity of contraction at fixed muscle length	• Is maximal when there is no afterload. • Is decreased by increasing afterload.

RATE-INDUCED REGULATION OF MYOCARDIAL CONTRACTION

- **Rate - Induced Regulation**
  - A sustained change in contraction frequency affects the strength of contraction by altering the rate of influx of Ca++ into the cell per minute
  - A transient change in contraction frequency alters contractile strength because an appreciable delay exists between the time that Ca++ is taken up by the sarcoplasmic reticulum and the time that it becomes available again for release.

FACTORS AFFECTING END-DIASTOLIC VOLUME

- Increase length of ventricular muscle fibers (Increase end-diastolic volume)
  - Stronger atrial contraction
  - Increased total blood volume
  - Increased venous tone
  - Increased pumping action of skeletal muscle
  - Increased negative intrathoracic pressure
- Decrease length of ventricular muscle fiber (Decrease end-diastolic volume)
  - Standing
  - Increased intrapericardial pressure
  - Decreased ventricular compliance i.e., an increase in ventricular stiffness produced by myocardial infarction, infiltrative disease.

FACTORS AFFECTING CARDIAC CONTRACTILITY

- **Increased heart rate**
  - increases contractility because more action potentials per unit time means more Ca++ entry into the myocardia ell, more Ca++ released from the SR, and greater tension produced during contraction
  - Examples of effect of heart rate are:
    - Positive staircase or Bowditch staircase.
      - ❖ Increased heart rate increases the strength of contraction in a stepwise fashion as the intracellular [Ca2+] increases over several beats.
    - Post-extrasystolic potentiation.
      - ❖ The beat following an extrasystolic beat has increased strength of contraction because of the increased intracellular [Ca++].
- **Catecholamines**
  - Exert their inotropic effect via an action on cardiac ß1 – adrenergic receptors and Gs, with resultant activation of adenylyl cyclase and increased intracellular cAMP.
- **Sympathetic & Parasympathetic Nerve Impulses**
  - Sympathetic stimulation via ß receptors increases the strength of contraction by two mechanisms :
    - It increases the entry of Ca++ into the cell during the plateau of each cardiac action potential.

        - It increases the activity of the Ca++ pump of the SR (phospholamban); therefore, more Ca++ will be accumulated and thus will be available for release in subsequent beats.
    - Parasympathetic stimulation (Ach) via muscarinic receptors decrease the strength of contraction in atria by decreasing Ca++ entry into the cell during the plateau of the cardiac action potential (inward Ca^{2+} current).
- **Cardiac Glycosides (Digitalis) and Other Inotropic Agents**
    - Digitalis increase the strength of contraction by inhibiting Na^+ - K^+ ATPase in the cardiac muscle cell.
        - As a result, the intracellular Na^+ rises, diminishing the Na^+ gradient across the cell membrane.
        - Ca^{2+} - Na^+ exchange (a mechanism that extrudes $Ca2^+$ from the cell) depends on the size of this Na^+ gradient and is diminished, causing a rise in the intracellular Ca^{2+}.
    - Xanthines such as caffeine and theophylline inhibit the breakdown of camp. These agents are positively inotropic.
    - Glucagon increases the formation of cAMP, and is positively inotropic.
- Other Pharmacologic Agents
    - Quinidine, procainamide, and barbiturates depress myocardial contractility.

EFFECT OF TEMPERATURE ON CARDIAC FUNCTION

- Increased temperature (fever) greatly increased the heart rate.
- Decreased temperature greatly decreased the heart rate.
- Mechanism:
    - Heat causes increased permeability of the cardiac muscle membrane to the controlling ions, resulting in acceleration of the self-excitation process.
- Contractile strength of the heart is enhanced temporarily by a moderate increase in temperature, but prolonged elevation of the temperature exhausts the metabolic systems of the heart and eventually causes weakness.
- Optimal function of the heart depends greatly on proper control of the body temperature by the temperature control mechanism.

	SYMPATHETIC		PARASYMPATHETIC	
	Effect	**Receptor**	**Effect**	**Receptor**
Heart Rate	↑	β1	↓	Muscarinic
Conduction Velocity (AV Node)	↑	β1	↓	Muscarinic
Contractility	↑	β1	↓ (atria only)	Muscarinic
Vascular Smooth Muscle	Constriction			
Skin, Splanchine	Constriction	α		
Skeletal Muscle	Relaxation	β2		

MECHANISMS IN CARDIAC EXTRINSIC REGULATION

NERVOUS CONTROL OF CARDIAC ACTIVITY

- The control of the heart by the sympathetic and parasympathetic neurons
- Action potentials in these neurons trigger the release of norepinephrine, which binds to ß - adrenergic receptors on the surface of heart muscle cells. This causes the activation of adenylate cyclase, the enzyme that catalyzes formation of cyclic AMP from ATP. The resulting increase in cyclic AMP levels in the muscle cell alters the function of plasma membrane calcium channels, such that the amount of calcium entering cells with each action potential increases. The end result is a general increase in intracellular calcium concentration, which has a two-fold effect:
    - Binding of calcium to troponin increases, which results in more active cross bridges and more contractile force
    - Calcium ion triggers an increase in the calcium permeability of the sarcoplasmic reticulum, which increases the amount of calcium released during an action potential
- Sympathetic stimulation via B receptor:
    - ↑ heart rate
    - ↑ conduction velocity (AV node)
    - ↑ force of heart contraction
    - ↑ cardiac output
- Parasympathetic stimulation via muscarinic receptor:
    - ↓ heart rate
    - ↓ conduction velocity (AV node)
    - ↓ contractility (atria only)
    - ↓ cardiac output

CHEMICAL CONTROL OF CARDIAC ACTIVITY

- **Hormones**
    - Epinephrine, the principal hormone secreted by the adrenal medulla, binds to ß receptors on the heart muscle cells and affects intracellular cAMP levels. It increases myocardial contractility, thereby promoting increases in stroke volume and cardiac output.
    - Thyroid hormones affect the composition of myosin isoenzymes in cardiac muscle. By increasing these isoenzymes with the greatest ATPase activity, thyroid hormones enhance myocardial contractility.
    - Insulin has a prominent, direct, positive inotropic effect on the heart. Its positive inotropic effect is potentiated by ß - adrenergic receptor antagonists.
    - Glucagon has potent positive inotropic and chronotropic effects on the heart. Its effects on the heart closely resemble those of the catecholamines and certain metabolic effects are similar.
        - Both glucagons and catecholamines activate adenylyl cyclase to increase myocardial tissue levels of cyclic AMP. The consequent rise in cAMP increases Ca++ influx through the Ca++ channels in the sarcolemma, and facilitates Ca++ release and receptake by the sarcoplasmic reticulum.
- **Blood Gases**
    - Changes in oxygen tension (PaO_2) of the blood perfusing the brain and the peripheral chemoreceptors affect the heart through nervous mechanisms. These indirect effects of hypoxia are usually prepotent. When a subject is exposed to moderate degrees of hypoxia, heart rate, cardiac output, and myocardial contractility are usually enhanced.
    - The PO2 of the arterial blood perfusing the myocardium also influences myocardial performance directly.
        - The effect of hypoxia is biphasic: mild hypoxia is stimulatory, but more severe hypoxia is depressant because oxidative metabolism is limited.
    - Changes in $PaCO_2$ may also affect the myocardium directly and indirectly.
        - The direct effects on the heart elicited by changes of PCO2: decreasing it to 34 mmHg increases the left ventricular systolic pressure (stimulatory), whereas increasing it to 86 mm has the reverse effect (depressant).
        - The indirect, neurally mediated effects produced by an increased PCO_2 in the systemic arterial blood are similar to those evoked by a decrease in PaO_2. The effect of moderate increase in systemic arterial PCO_2 on the CVS is to increase heart rate, cardiac output, and arterial blood pressure.
        - Neither the arterial PCO_2, nor the blood pH is a primary determinant of myocardial behavior; the associated change in intracellular pH is the critical factor.
            - ❖ The reduced intracellular pH diminishes the amount of Ca++ released from the sarcoplasmic reticulum in response to excitation. The diminished pH also decreases the sensitivity of the myofilaments to Ca++.
            - ❖ Increases in intracellular pH have the opposite effect; that is, they enhance the sensitivity to Ca++.

- **Effect of Ions**
  - **Potassium Ions**
    - Excess K+ in the extracellular fluids causes the following:
      - ❖ Heart becomes dilated and flaccid
      - ❖ Decrease heart rate
      - ❖ Block conduction of the cardiac impulse from the atria to the ventricles thru the A-V bundle.
    - Mechanism:
      - ❖ High K+ concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fiber. As the membrane potential decreases, the intensity of action potential also decreases, which makes contraction of the heart progressively weaker.
  - **Calcium Ions**
    - Excess of calcium ion causes the heart to go toward spastic contraction. This is caused by the direct effect of Ca++ ions in exciting the cardiac contractile process
    - Deficiency of Ca++ ion causes cardiac flaccidity, similar to the effect of high K.

SOURCE OF ENERGY REQUIRED FOR CARDIAC CONTRACTILITY

- Heart muscle, like skeletal muscle, uses chemical energy to provide work for contraction.
- This energy is derived mainly from oxidative metabolism of fatty acids and, to a lesser extent of other nutrients, especially lactate and glucose.

FACTORS THAT INCREASE CARDIAC OXYGEN CONSUMPTION

- The O_2 consumption of the heart is determined primarily by the intramyocardial tension, the contractile state of the myocardium, and the heart rate.
- Is increased by:
  - increased afterload (aortic pressure)
  - increased size of the heart (law of Laplace: tension is proportional to radius)
  - increased contractility
  - increased heart rate
  - can be expressed by the following equation:
  - cardiac output = stroke volume X heart rate
- The work done by the heart is the product of stroke volume and mean arterial pressure in the pulmonary artery (for the right ventricle) or the aorta (for the left ventricle) and can be expressed by the following equation :
- Stroke work = stroke volume x aortic pressure or mean arterial pressure
- Fatty acids are the primary source of energy for stroke work.