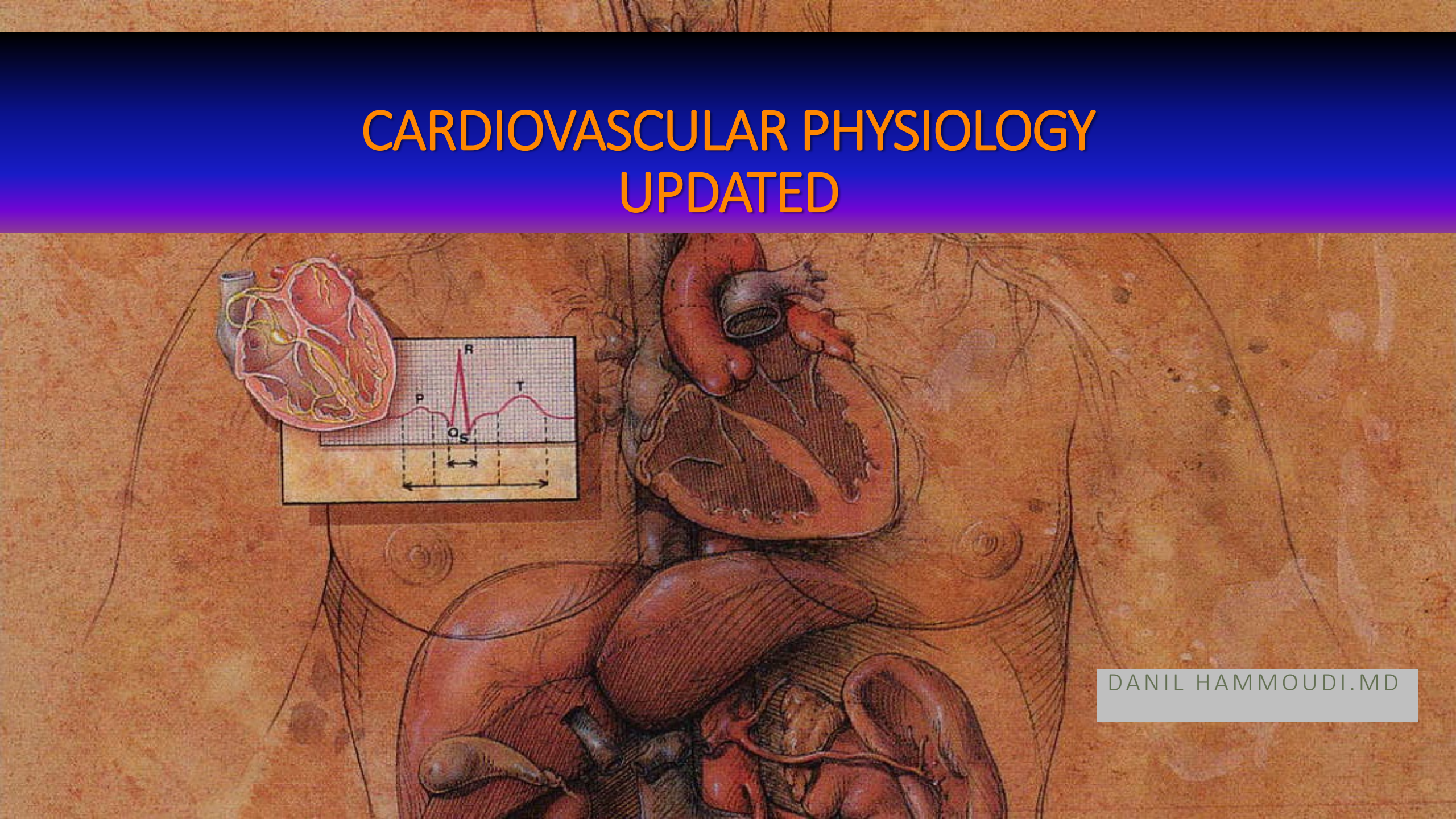
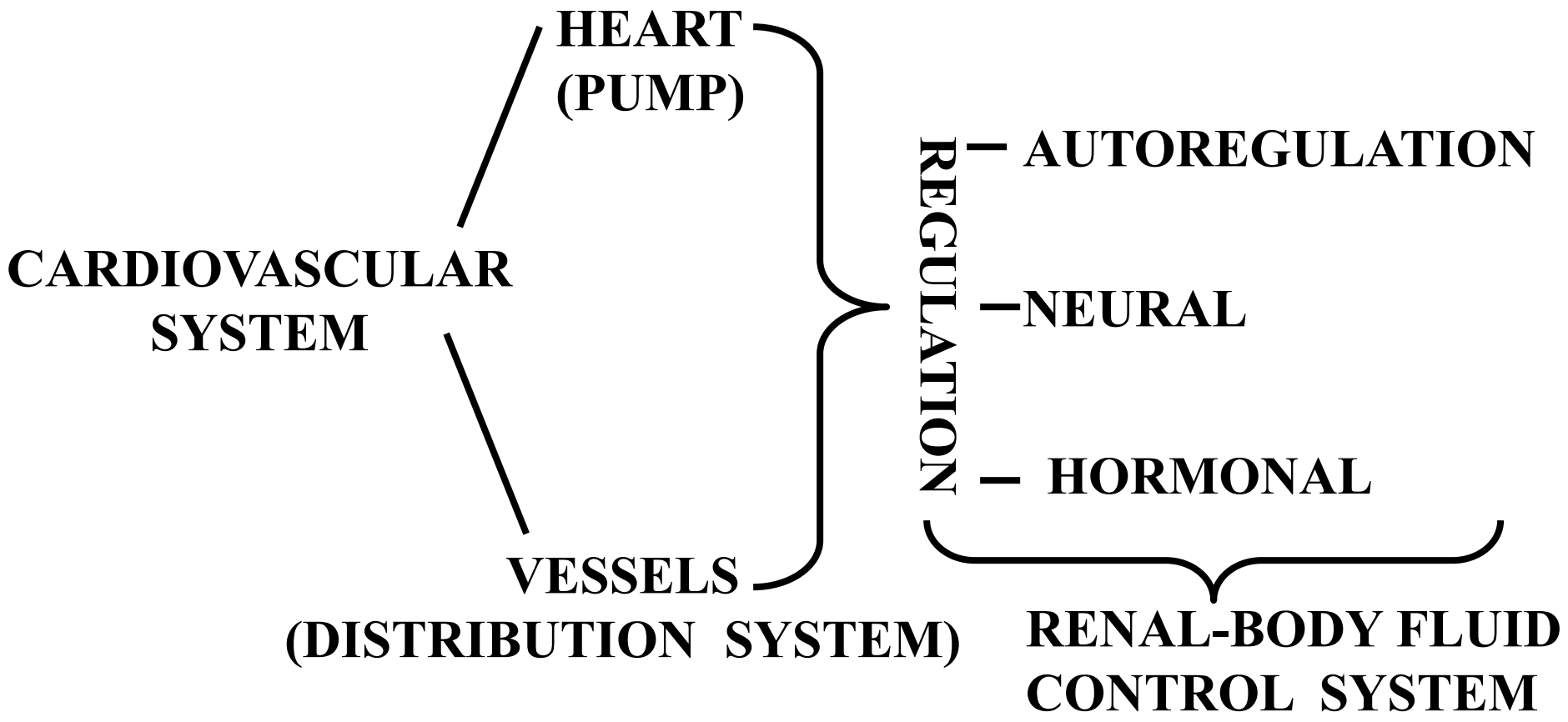
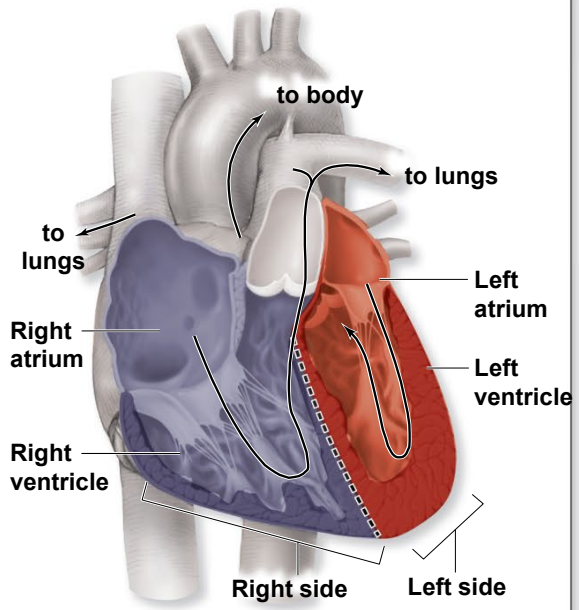
CARDIOVASCULAR PHYSIOLOGY UPDATED



DANIL HAMMOUDI.MD


HEART
(PUMP)
CARDIOVASCULAR
SYSTEM
VESSELS
(DISTRIBUTION SYSTEM)
REGULATION
AUTOREGULATION
NEURAL
HORMONAL
RENAL-BODY FLUID
CONTROL SYSTEM

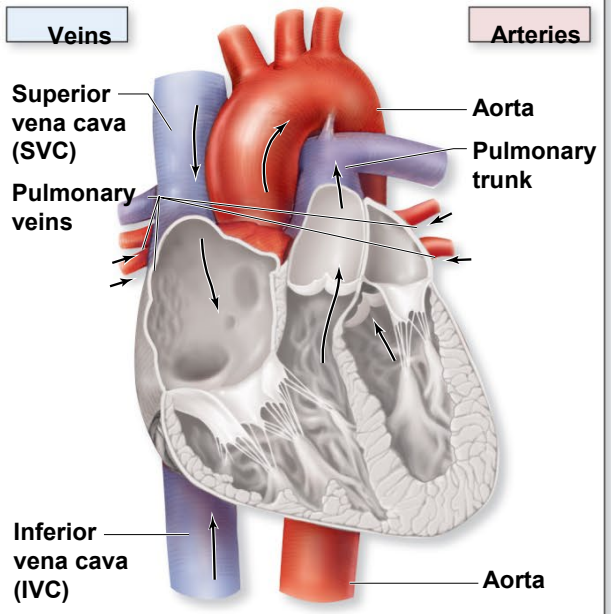


Two pumps

Each pump has a receiving chamber (atrium) and a pumping chamber (ventricle).

- Right side: pumps deoxygenated blood to the lungs
- Left side: pumps oxygenated blood to the body

(a)



Great vessels

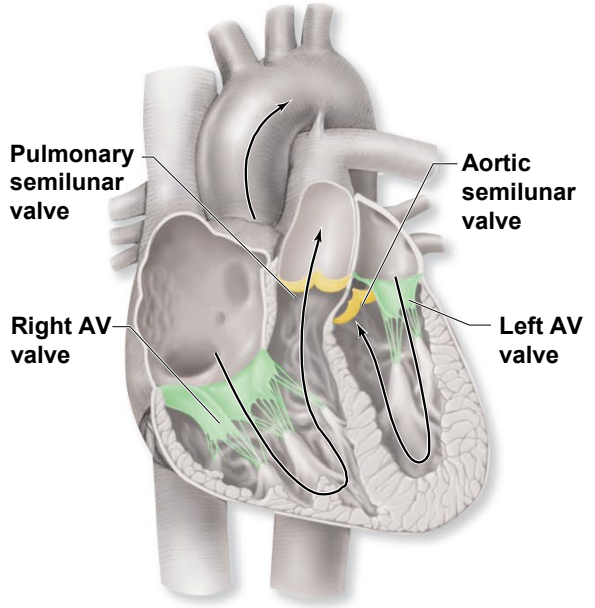
Arteries (arterial trunks) transport blood away from the heart.

- Pulmonary trunk transports from right side
- Aorta transports from left side

Veins transport blood toward the heart

- Vena cavae (SVC and IVC) drain into right side
- Pulmonary veins drain into left side

(b)



Valves

Heart valves prevent backflow to ensure one-way blood flow.

- Atrioventricular (AV) valves (i.e., right AV valve and left AV valve) are between atrium and ventricle
- Semilunar valves (i.e., pulmonary semilunar valve and aortic semilunar valve) are between ventricle and arterial trunk

(c)

Coronary Blood Flow

coronary blood flow: 250 ml/min

5% of resting cardiac output

60-80 ml blood/100g tissue/min

entirely during diastole

- ~ aortic diastolic pressure minus LVDP
- ~ duration of diastole

pressure < 150 mmHg

oxygenated by superb membrane oxygenator-"the lungs"

Cerebral Blood Flow

- Cerebral blood flow: 750 ml/min
- 15% of resting cardiac output
- 50-55 ml blood/100g tissue/min

Heart HORMONES

Natriuretic Peptides

In response to a rise in blood pressure, the heart releases two peptides:

- **A-type Natriuretic Peptide** (ANP)
  - ❑ This hormone of 28 amino acids is released from stretched **atria** (hence the "A").
- **B-type Natriuretic Peptide** (BNP)
  - ❑ This hormone is released from the **ventricles**. (It was first discovered in brain tissue; hence the "B".)

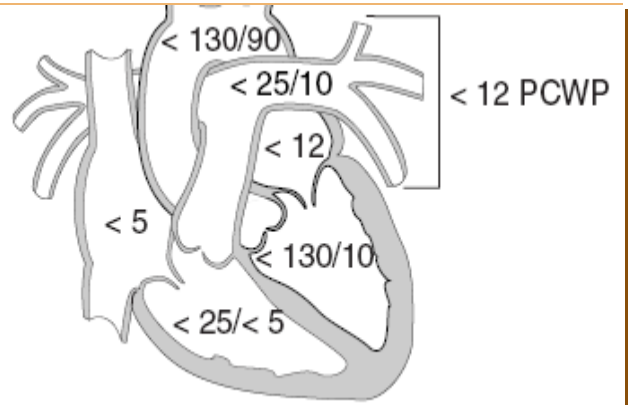
Both hormones lower blood pressure by :

- **relaxing arterioles**
- **inhibiting the secretion of renin and aldosterone**
- **inhibiting the reabsorption of sodium ions by the kidneys.**

- The latter two effects reduce **the reabsorption of water by the kidneys**.
  - =➔So the volume of urine increases as does the amount of sodium excreted in it.
  - The net effect of these actions is to **reduce blood pressure by reducing the volume of blood in the circulatory system.**

- These effects give ANP and BNP their name (natrium = sodium; uresis = urinate).

Normal pressures



- **Pulmonary capillary wedge pressure (PCWP;in mm Hg) is a good approximation of left atrial pressure.**
- In mitral stenosis, PCWP > LV end diastolic pressure.
- PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

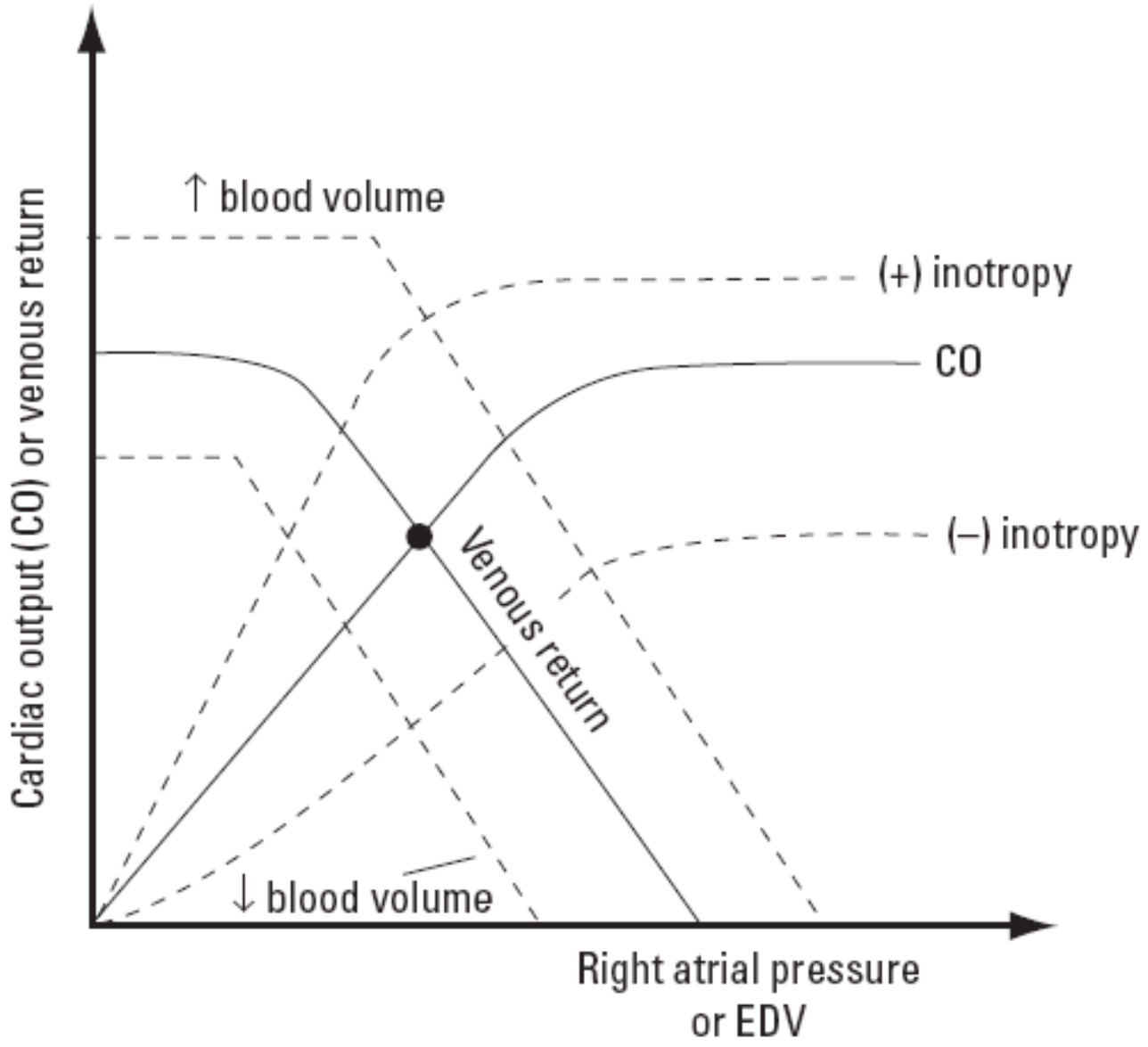
Cardiac myocyte physiology

Cardiac muscle contraction is dependent on extracellular calcium, which enters the cells during plateau of action potential and stimulates calcium release from the cardiac muscle sarcoplasmic reticulum (calcium-induced calcium release).

In contrast to skeletal muscle:

1. Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx
2. Cardiac nodal cells spontaneously depolarize, resulting in automaticity
3. Cardiac myocytes are electrically coupled to each other by gap junctions

Cardiac and vascular function curves



Differences Between Skeletal and Cardiac Muscle Physiology

Action Potential

- **Cardiac:** Action potentials conducted from cell to cell.
- **Skeletal**, action potential conducted along length of single fiber

Rate of Action Potential Propagation

- Slow in cardiac muscle because of gap junctions and small diameter of fibers.
- Faster in skeletal muscle due to larger diameter fibers.

Calcium release

- Calcium-induced calcium release (CICR) in cardiac
  - Movement of extracellular Ca^{2+} through plasma membrane and T tubules into sarcoplasm stimulates release of Ca^{2+} from sarcoplasmic reticulum
- Action potential in T-tubule stimulates Ca^{++} release from sarcoplasmic reticulum

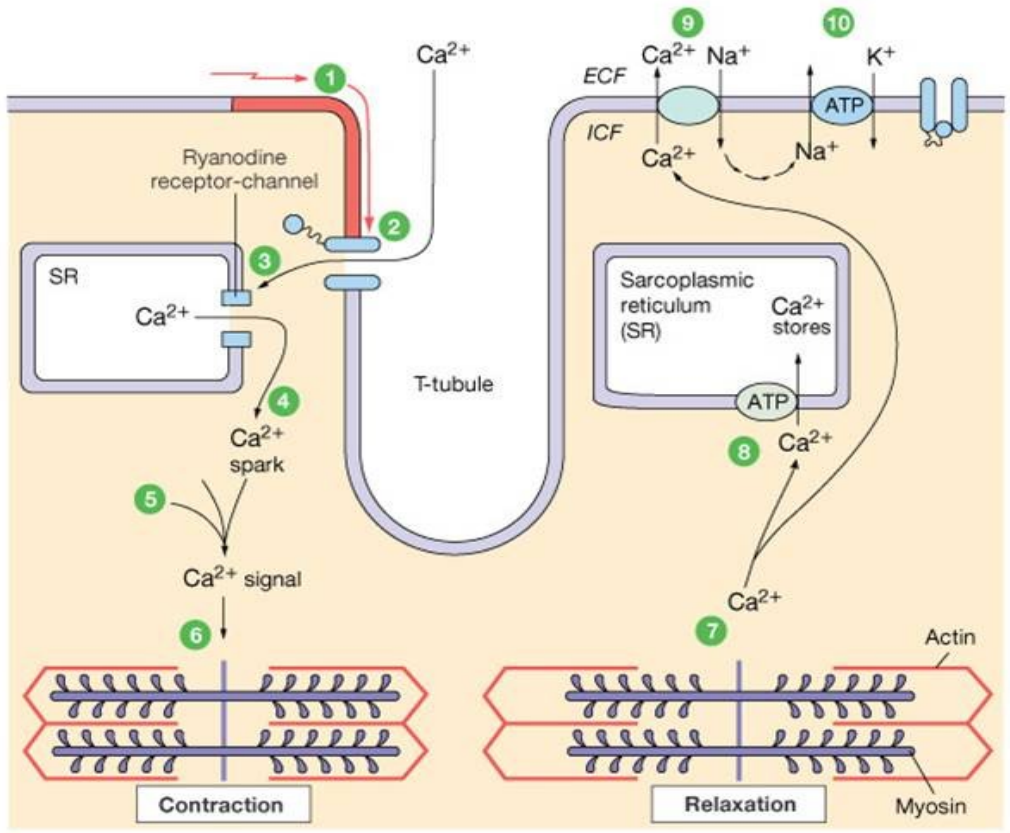
Cardiac Muscle Contraction

Heart muscle:

- Is stimulated by nerves and is self-excitable (automaticity)
- **Contracts as a unit**
- **Has a long (250 ms) absolute refractory period**
- pacemaker can funciton for many years without interruption

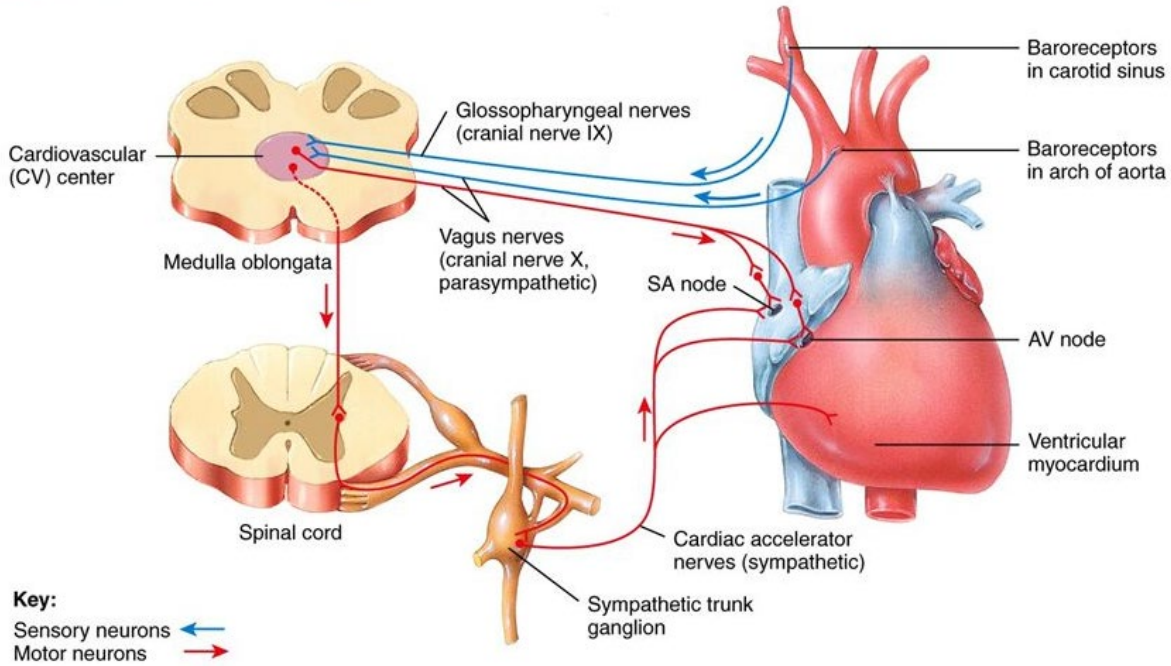
- **Ach** (**from ParaSym terminals** of **vagus nerve Xth cranial nerve**) =➔slows HR **by increasing K+** conductance & **reducing Ca2+ conductance of pacemaker cells**
- **Norepinephrine** (Sym NS) accelerates pacemaker potential = increasing HR

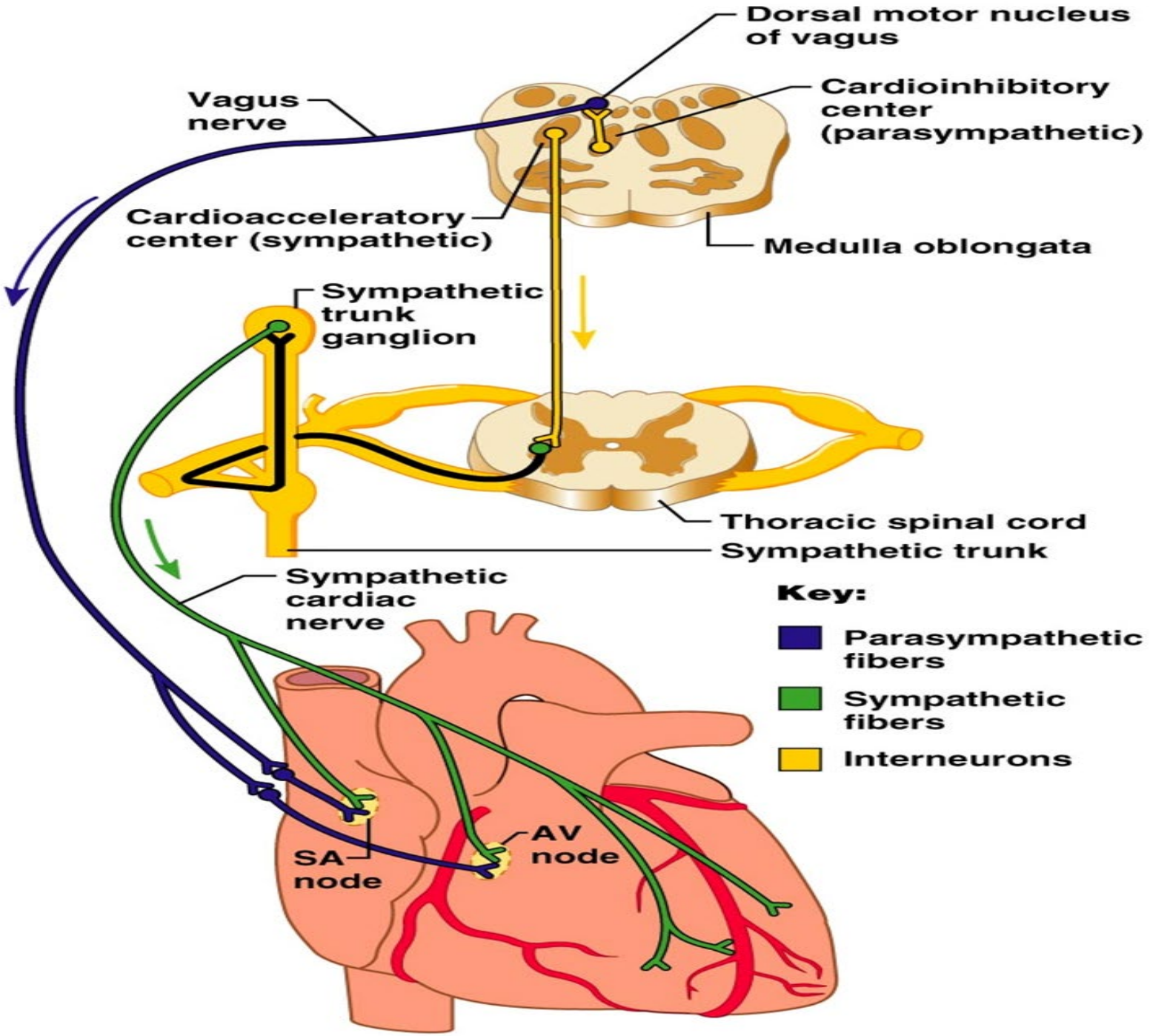
Cardiac muscle contraction is similar to skeletal muscle contraction



1. Action potential enters from adjacent cell.
2. Voltage-gated Ca^{2+} channels open. Ca^{2+} enters cell.
3. Ca^{2+} induces Ca^{2+} release through ryanodine receptor-channels (RyR).
4. Local release causes Ca^{2+} spark.
5. Summed Ca^{2+} sparks create a Ca^{2+} signal.
6. Ca^{2+} ions bind to troponin to initiate contraction.
7. Relaxation occurs when Ca^{2+} unbinds from troponi
8. Ca^{2+} is pumped back into the sarcoplasmic reticulum for storage.
9. Ca^{2+} is exchanged with Na^{+}.
10. Na^{+} gradient is maintained by the Na^{+}-K^{+}-ATPase.

Autonomic Nervous System Regulation of Heart Rate




Dorsal motor nucleus of vagus
Vagus nerve
Cardioinhibitory center (parasympathetic)
Cardioacceleratory center (sympathetic)
Medulla oblongata
Sympathetic trunk ganglion
Thoracic spinal cord
Sympathetic trunk
Sympathetic cardiac nerve
Key:
Parasympathetic fibers
Sympathetic fibers
Interneurons
SA node
AV node

Autonomic innervation of the heart

- The autonomic nervous system is able to regulate the heart action in the long term.
- Sympathetic fibers innervate both the atria and ventricles.
- Parasympathetic fibers only innervate the atria.
- The sympathetic nerve can therefore even alter the contraction force of the chambers (inotropy).

•**Definition**: Modulation of cardiac action by sympathetic and/or parasympathetic nerve fibers
•**Aim**: Long-term regulation of heart action
•**Basic terms**

- **Chronotropy**: Any influence on the heart rate.
- **Dromotropy**: Any influence on the conductivity of cardiac tissue.
- **Inotropy**: Any influence on the force of cardiac muscle contraction.
- **Lusitropy**: Any influence on the rate of relaxation of cardiac muscle.
- **Bathmotropy**: Any influence on excitability of the heart muscle.

Basic terms

Chronotropy: Any influence on the heart rate.

Dromotropy: Any influence on the conductivity of cardiac tissue.

Inotropy: Any influence on the force of cardiac muscle contraction.

Lusitropy: Any influence on the rate of relaxation of cardiac muscle.

Bathmotropy: Any influence on excitability of the heart muscle.

SNS RECEPTOR TYPES AND LOCATION

What are the SNS receptor types in the following locations and what are their effects?

Heart

SA nodeα

β_1: increased pacemaker activity

AV node

β_1: increased conduction velocity

Myocardium

β_1: increased contractility

Vascular smooth muscle

Skin and splanchnic circuits

α_1 and α_2: constriction

Skeletal muscle and pulmonary circuits

β_2: dilation

Peripheral veins

Bronchioles

Bronchial muscle

β_2: dilates smooth muscle

Bronchial glands

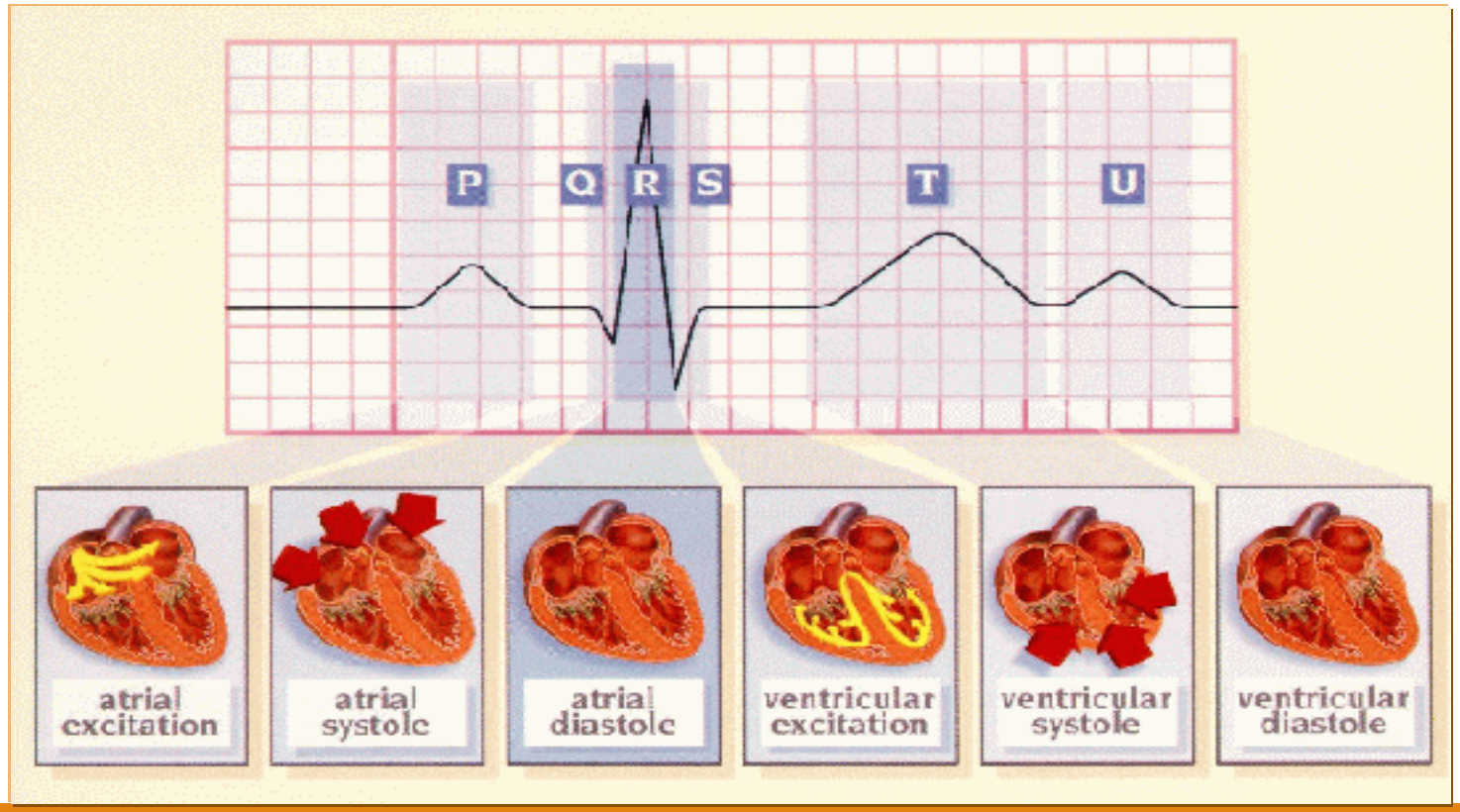
α_1: inhibits secretion

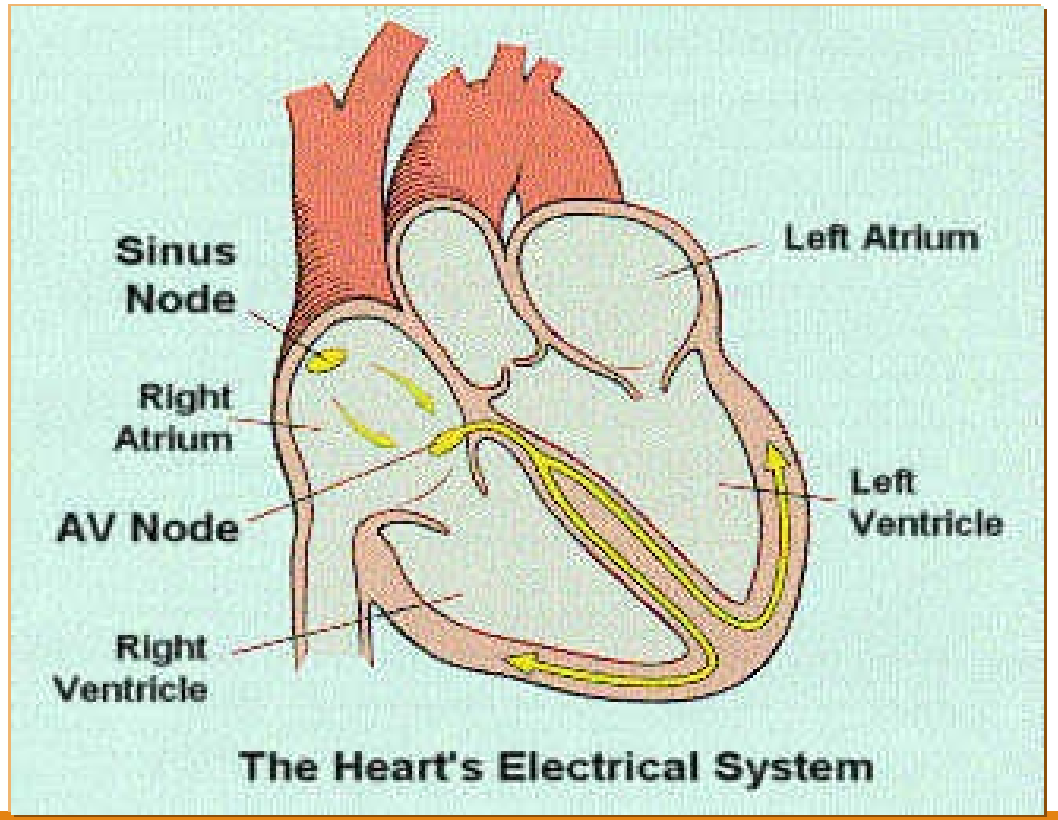
β_2: stimulates secretion

Heart Physiology: Intrinsic Conduction System

Autorhythmic cells:

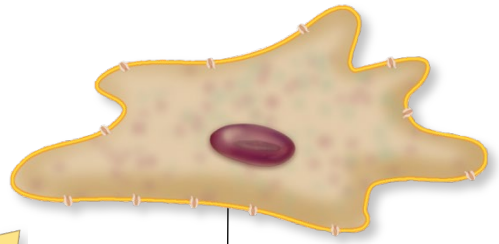
- Initiate action potentials
- Have unstable resting potentials called pacemaker potentials
- Use calcium influx (rather than sodium) for rising phase of the action potential



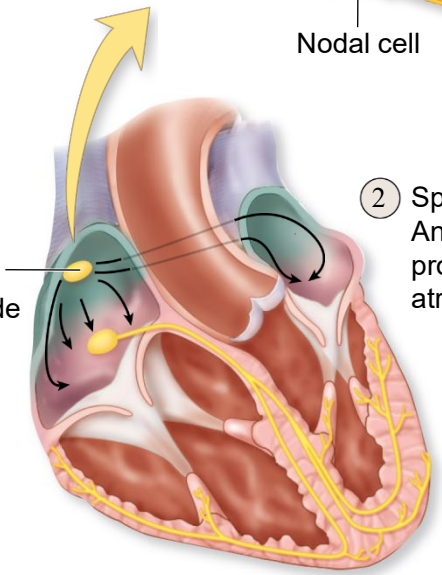


Conduction system

1 Initiation
SA node initiates action potential.



Nodal cell

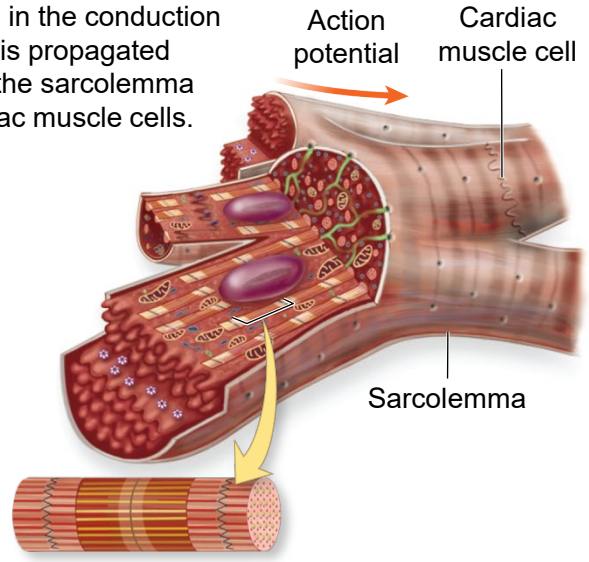


2 Spread of action potential
An action potential is propagated throughout the atria, the conduction system.

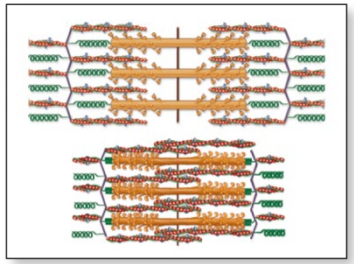
(a)

Cardiac muscle cells

1 The action potential initiated in the conduction system is propagated across the sarcolemma of cardiac muscle cells.



2 Muscle contraction
Thin filaments slide past thick filaments and sacromeres shorten within cardiac muscle cells.



Sarcomeres shorten.

(b)

PACEMAKERS (in order of their inherent rhythm)

- Sino-atrial (SA) node
- Atrio-ventricular (AV) node
- Bundle of His
- Bundle branches
- Purkinje fibers

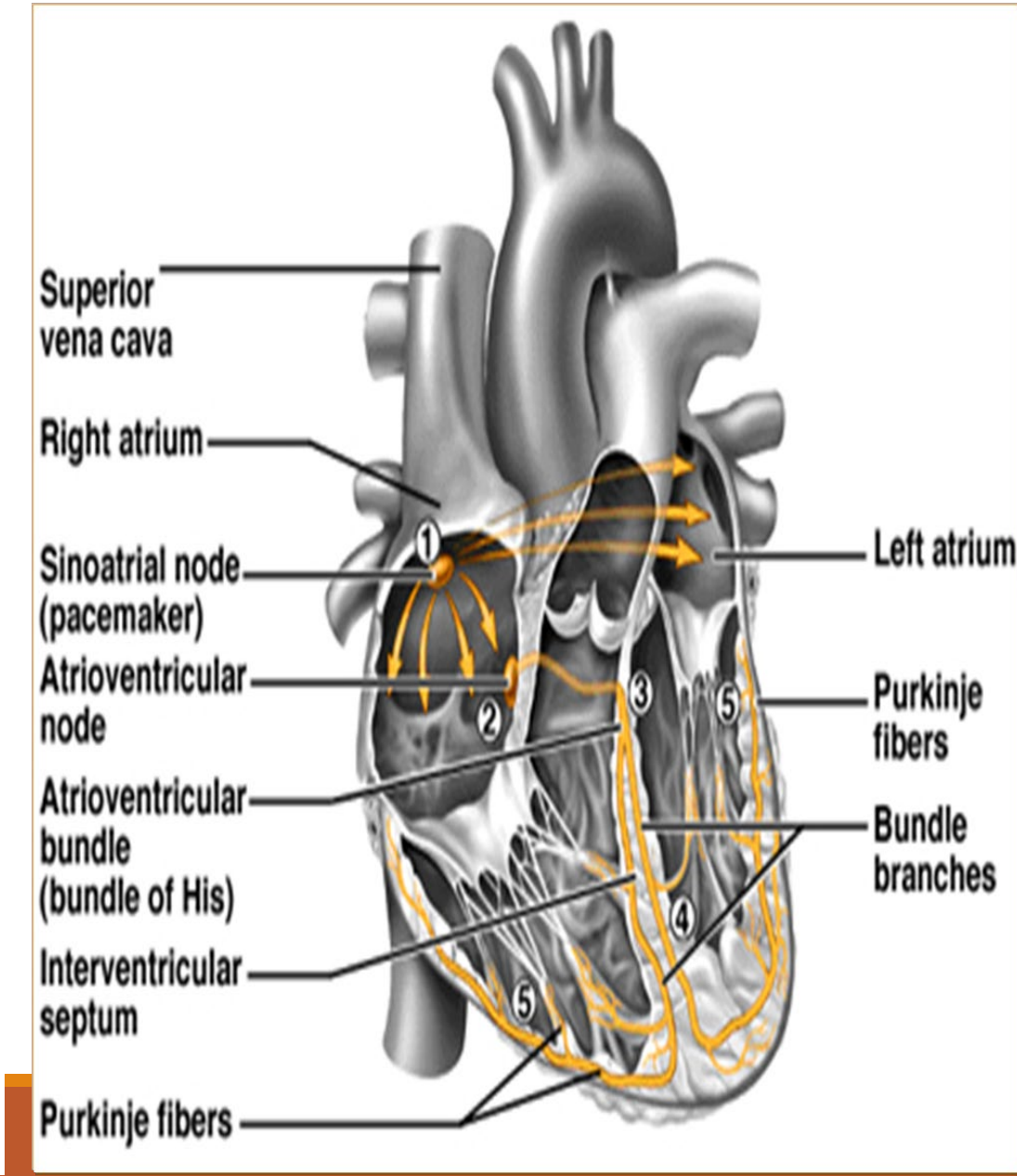
The autorhythmic cells are concentrated in the following areas.

•**The sinoatrial (SA) node**, located in the upper wall of the right atrium, initiates the cardiac cycle by generating an action potential that spreads through both atria through the gap junctions of the cardiac muscle fibers.

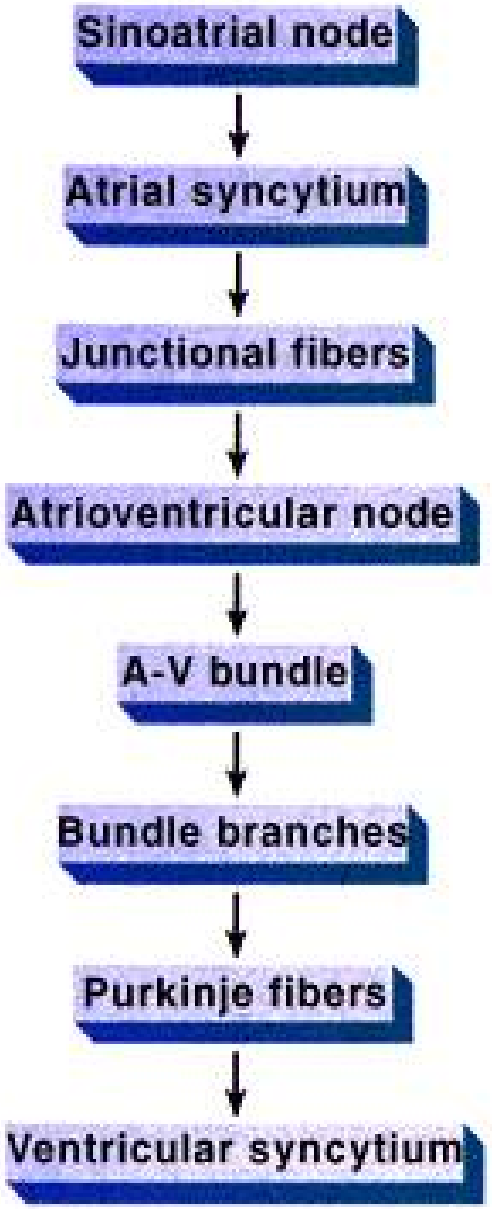
•**The atrioventricular (AV) node**, located near the lower region of the interatrial septum, receives the action potential generated by the SA node. A slight delay of the electrical transmission occurs here, allowing the atria to fully contract before the action potential is passed on to the ventricles.

•**The atrioventricular (AV) bundle (bundle of His)** receives the action potential from the AV node and transmits the impulse to the ventricles by way of the right and left bundle branches. Except for the AV bundle, which provides the only electrical connection, the atria are electrically insulated from the ventricles.

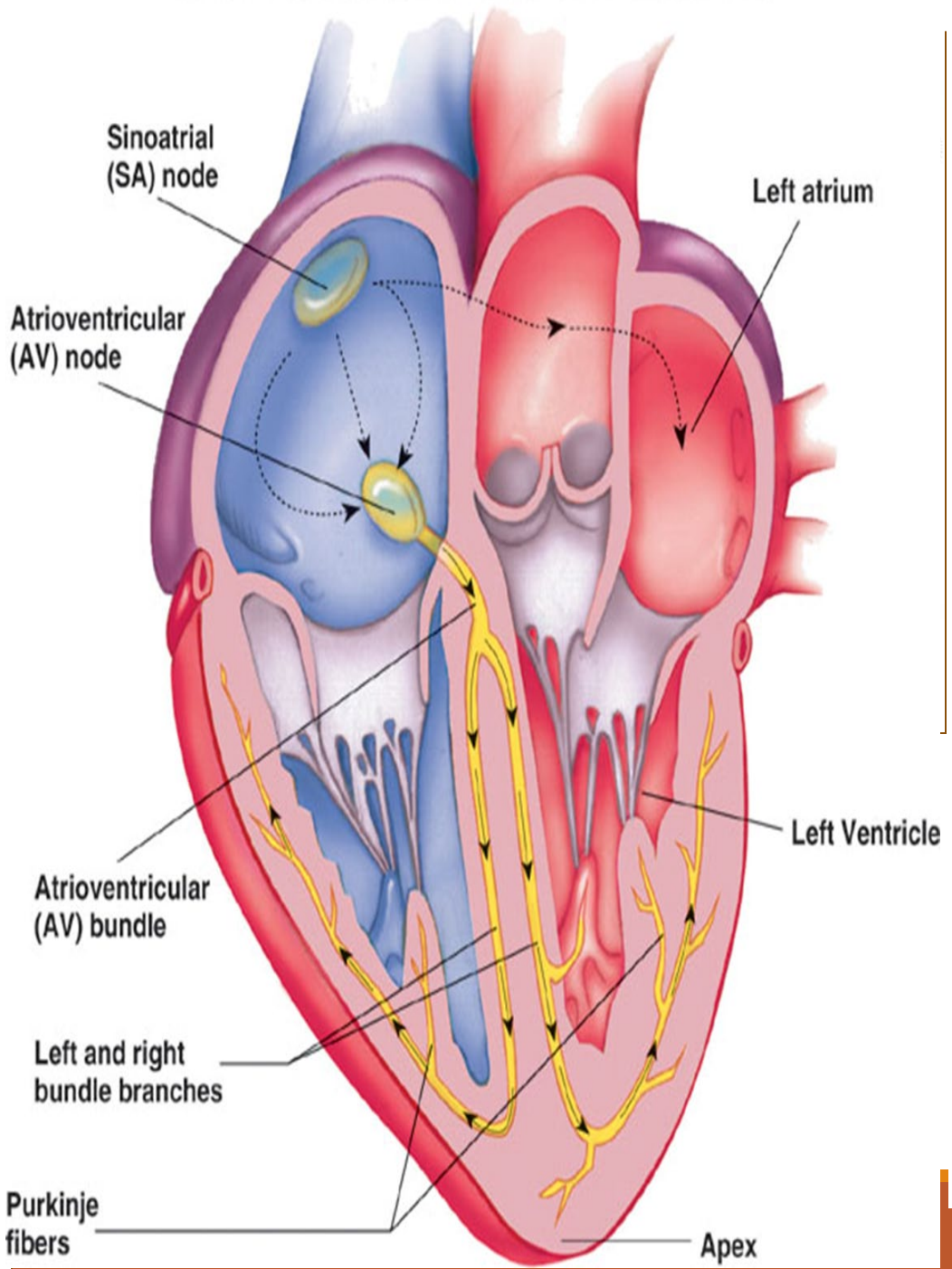
•**The Purkinje fibers** are large-diameter fibers that conduct the action potential from the interventricular septum, down to the apex, and then upward through the ventricles.



Cardiac Conduction System

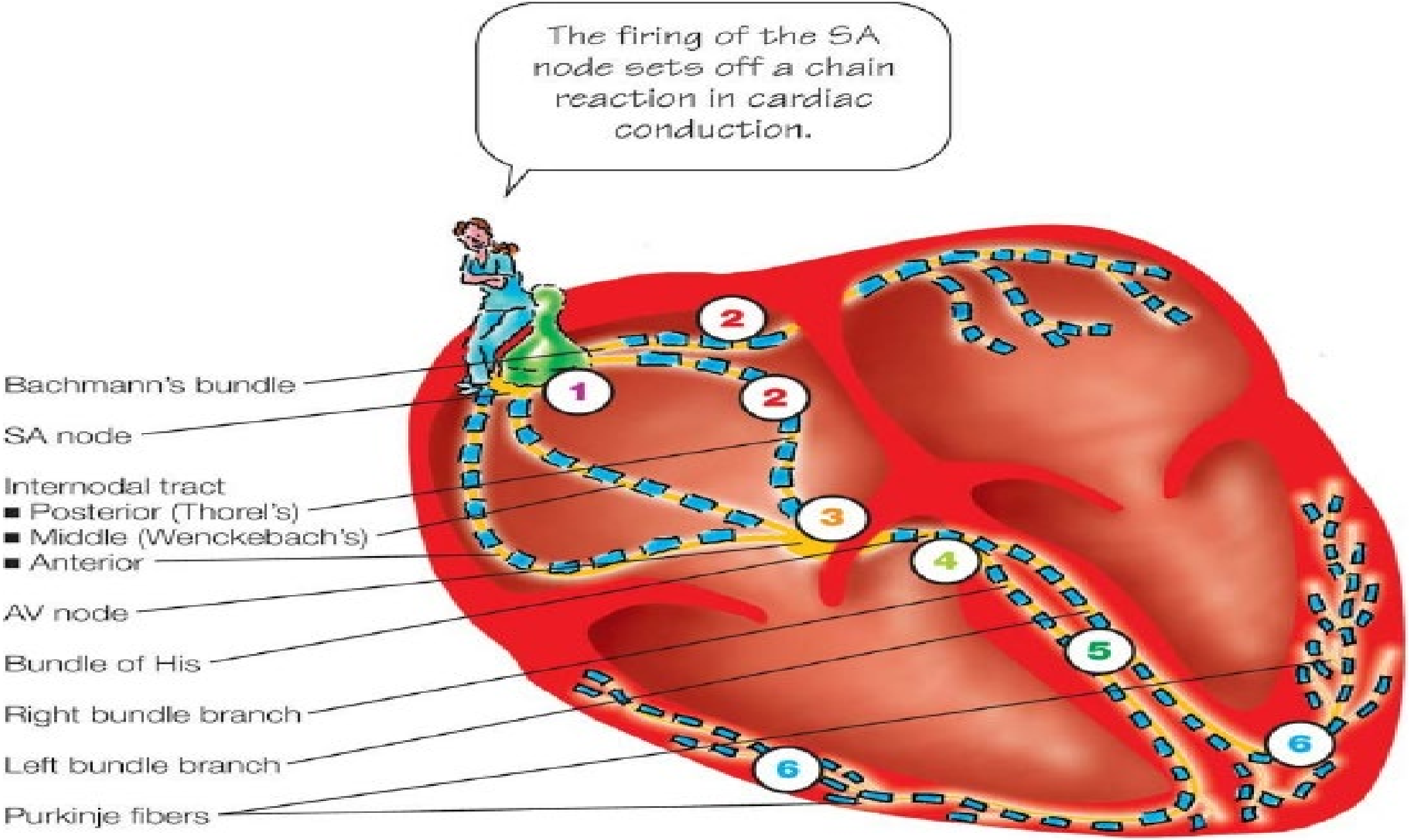


Hole's Human Anatomy and Physiology, 7th edition, by Shier, et al. copyright ©1996 TM Higher Education Group, Inc.

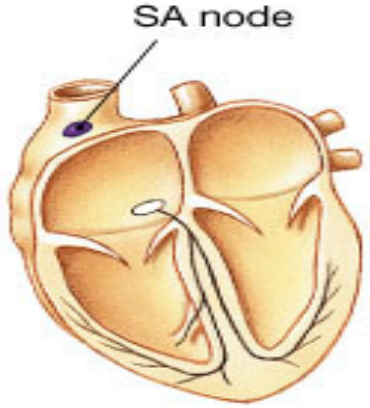


Sequence of excitation

1. **sinoatrial (SA) node - spreads to both atria**
   - 90 - 100 action potentials per minute
2. **atrioventricular (AV) node**
   - 40 -50 action potentials per minute
3. **atrioventricular (AV) bundle (bundle of His)**
   - 20-40 action potentials per minute
4. **right & left bundle branches**
   - in the interventricular septum
5. **Purkinje fibers**
   - conduction myofibers

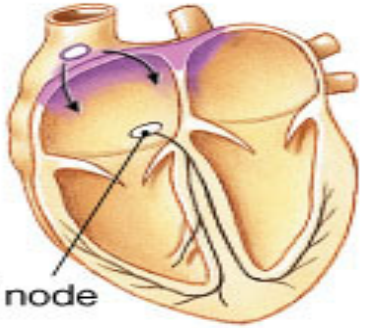

The firing of the SA node sets off a chain reaction in cardiac conduction.
Bachmann's bundle
SA node
Internodal tract
■ Posterior (Thorel's)
■ Middle (Wenckebach's)
■ Anterior
AV node
Bundle of His
Right bundle branch
Left bundle branch
Purkinje fibers
1
2
2
3
4
5
6
6

Impulse Conduction through the Heart



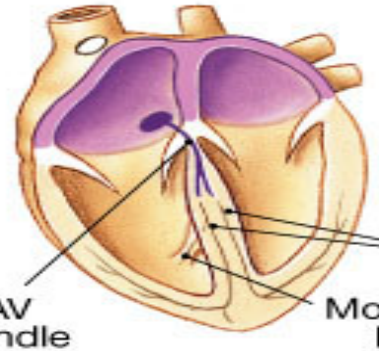
STEP 1:
SA node activity and atrial activation begin.

Time = 0



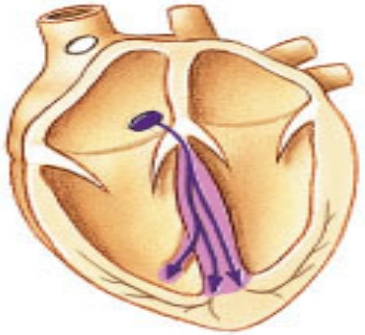
STEP 2:
Stimulus spreads across the atrial surfaces and reaches the AV node.

Elapsed time = 50 msec



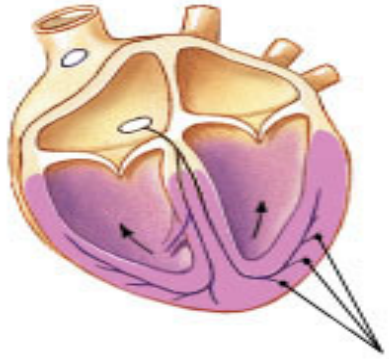
STEP 3:
There is a 100-msec delay at the AV node. Atrial contraction begins.

Elapsed time = 150 msec



STEP 4:
The impulse travels along the interventricular septum within the AV bundle and the bundle branches to the Purkinje fibers and, via the moderator band, to the papillary muscles of the right ventricle.

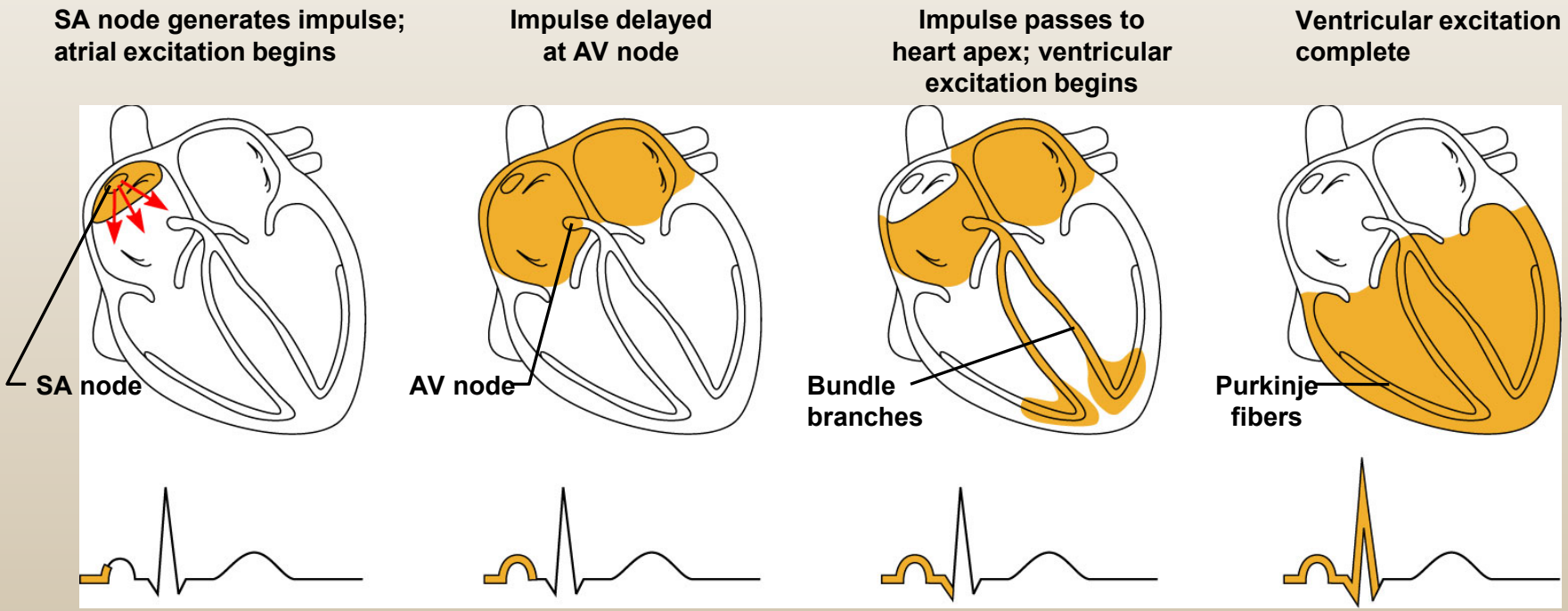
Elapsed time = 175 msec



STEP 5:
The impulse is distributed by Purkinje fibers and relayed throughout the ventricular myocardium. Atrial contraction is completed, and ventricular contraction begins.

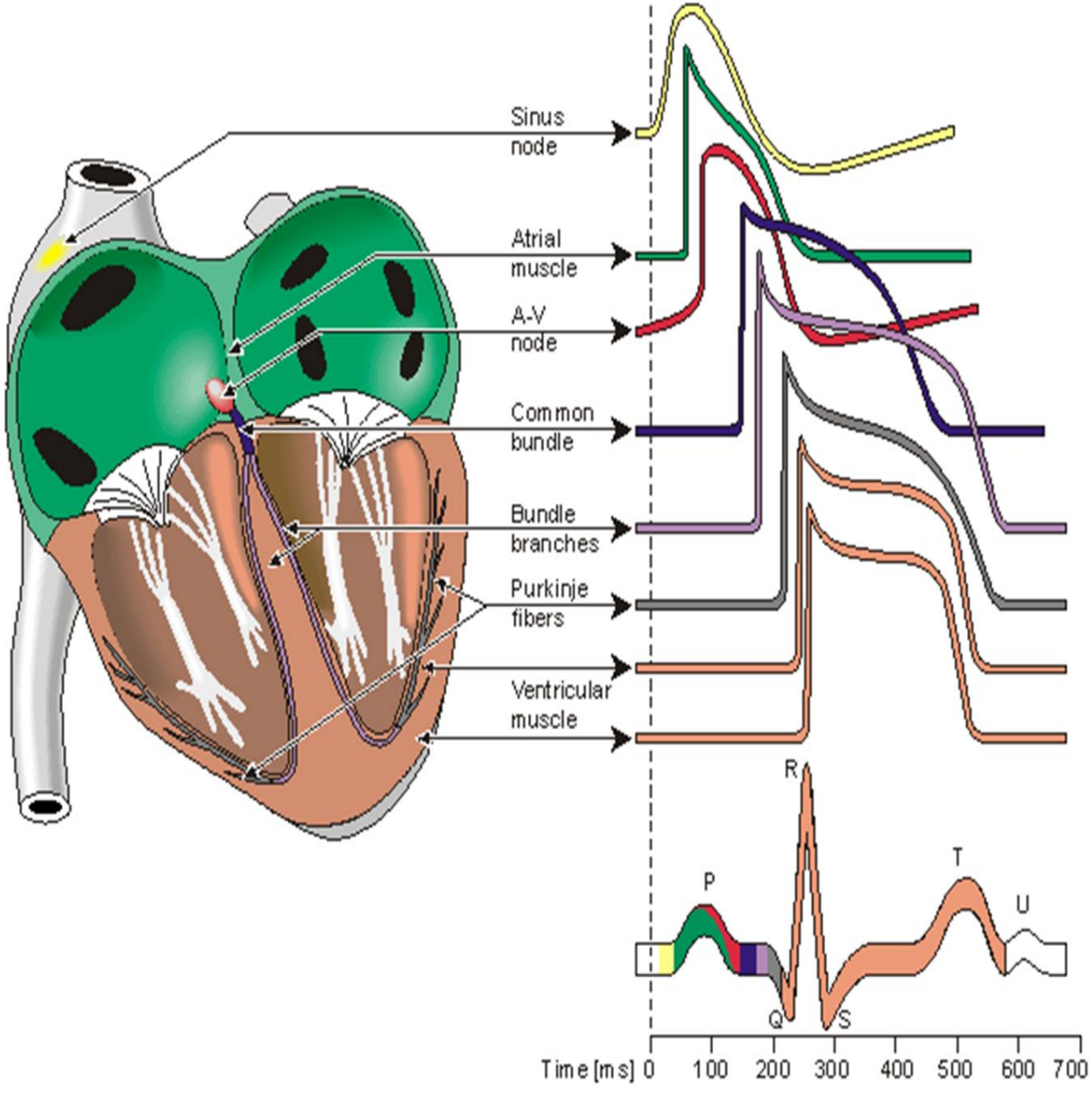
Elapsed time = 225 msec

Heart Excitation Related to ECG

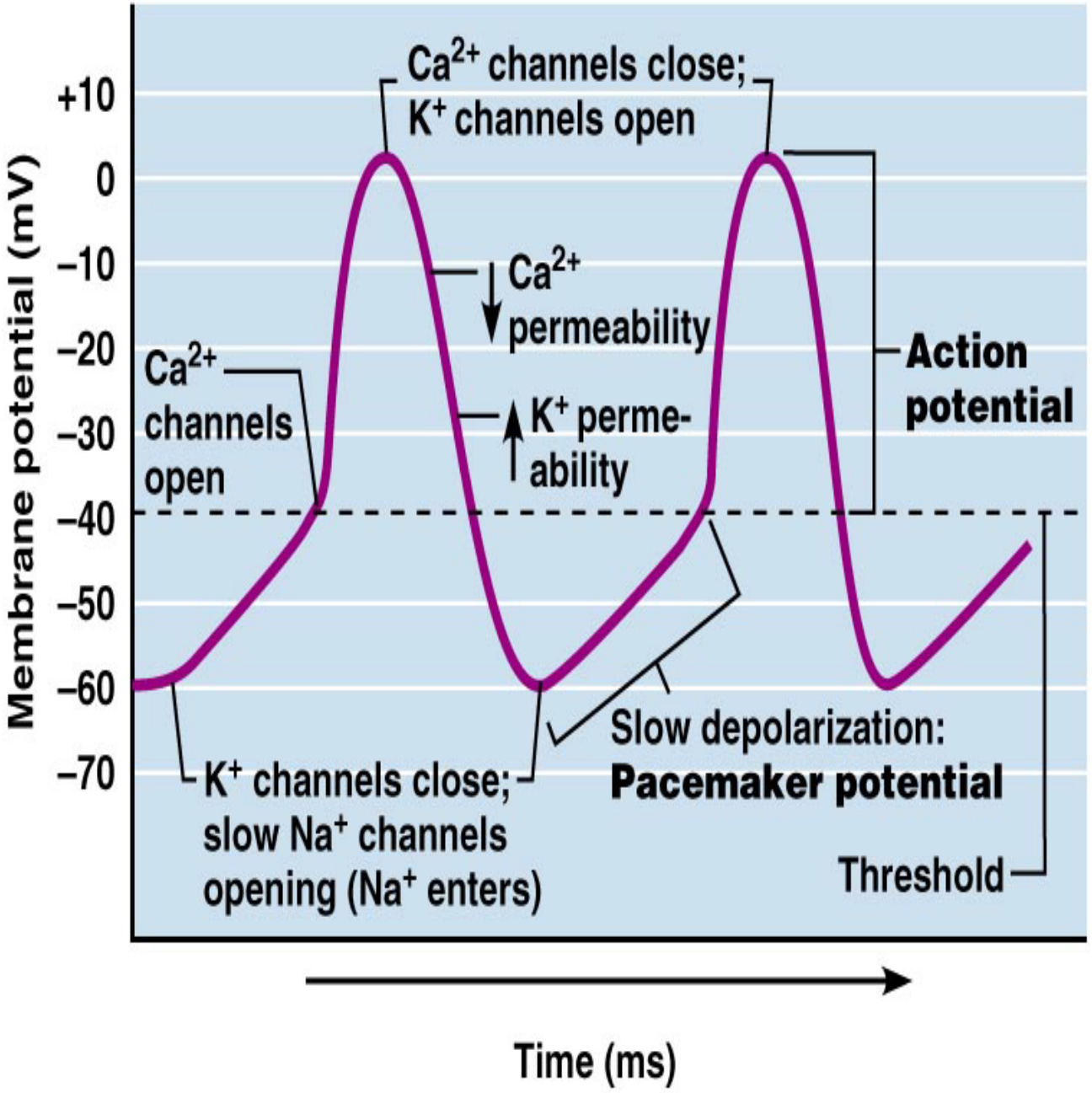


Depolarization of SA Node

- SA node - no stable resting membrane potential
- Pacemaker potential
  - gradual depolarization *from -60 mV*, slow influx of Na^+
- Action potential
  - *occurs at threshold of -40 mV*
  - *depolarizing phase to 0 mV*
    - *fast Ca^{2+} channels open, (Ca^{2+} in)*
  - *repolarizing phase*
    - *K^+ channels open, (K^+ out)*
    - *at -60 mV K^+ channels close, pacemaker potential starts over*
- Each depolarization creates one heartbeat
  - SA node at rest fires at 0.8 sec, about 75 bpm



Pacemaker and Action Potentials of the Heart



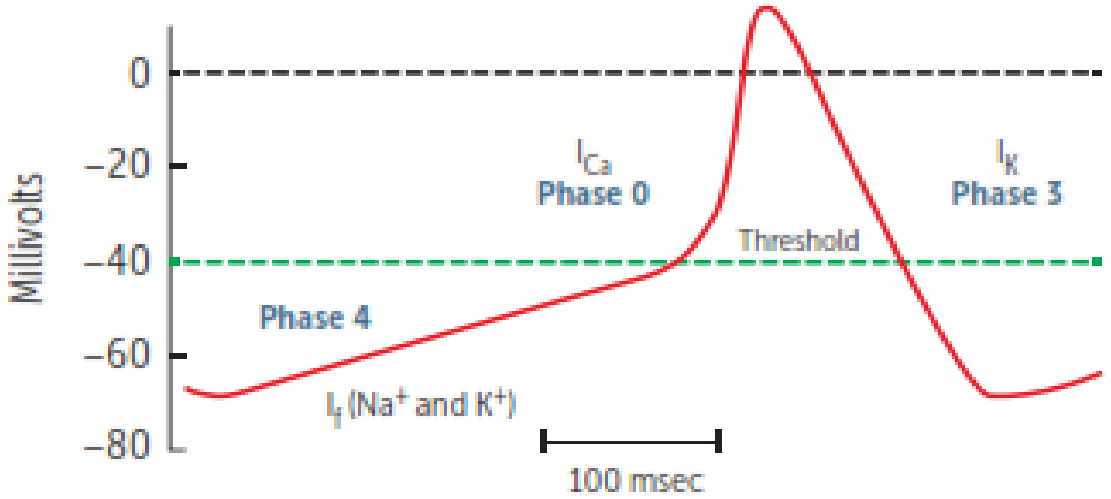
Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

Phase 0 = upstroke—opening of voltage-gated Ca^{2+} channels. Fast voltage-gated Na^+ channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

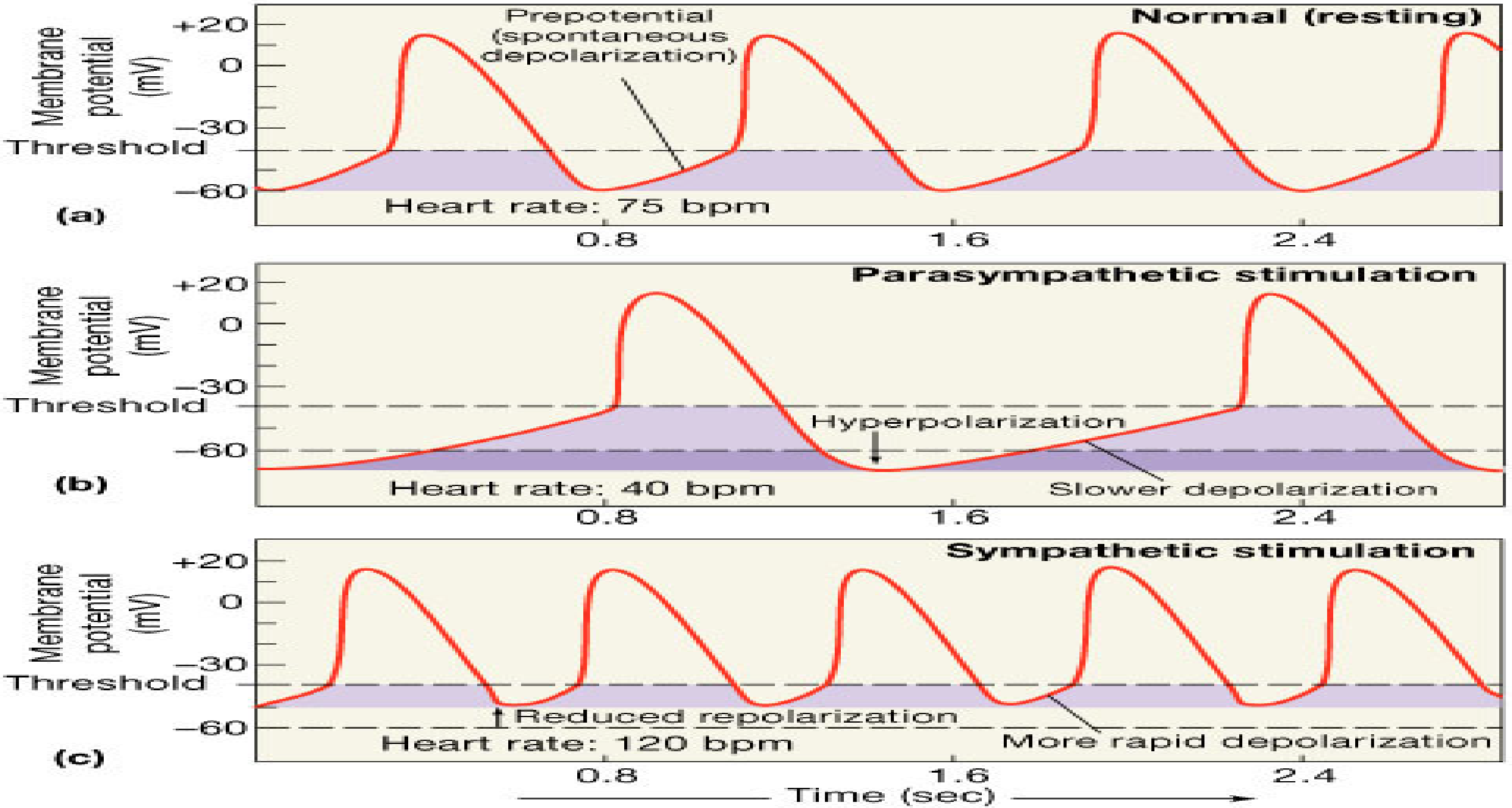
Phases 1 and 2 are absent.

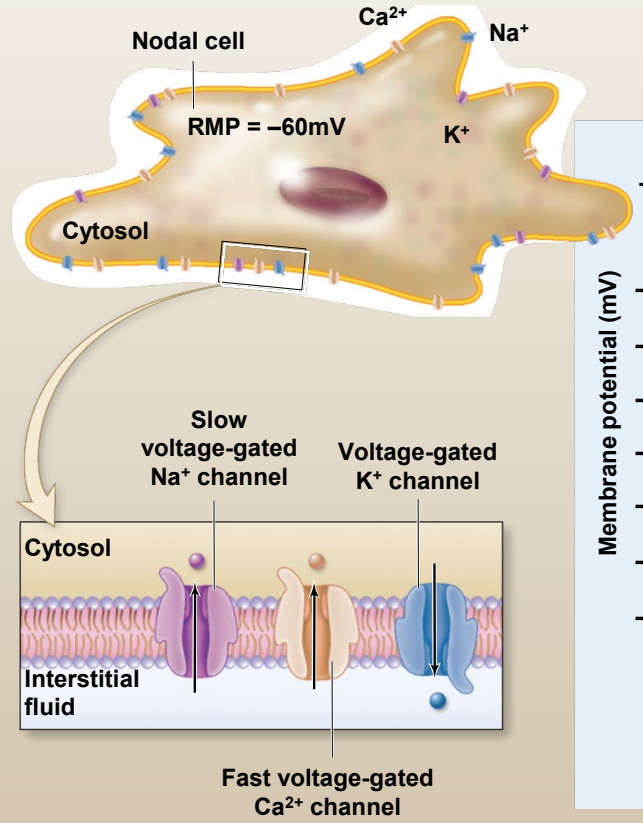
Phase 3 = repolarization—inactivation of the Ca^{2+} channels and ↑ activation of K^+ channels → ↑ K^+ efflux.

Phase 4 = slow spontaneous diastolic depolarization due to I_f ("funny current"). I_f channels responsible for a slow, mixed Na^+/K^+ inward current; different from I_{Na} in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that I_f channels are open and thus ↑ HR.

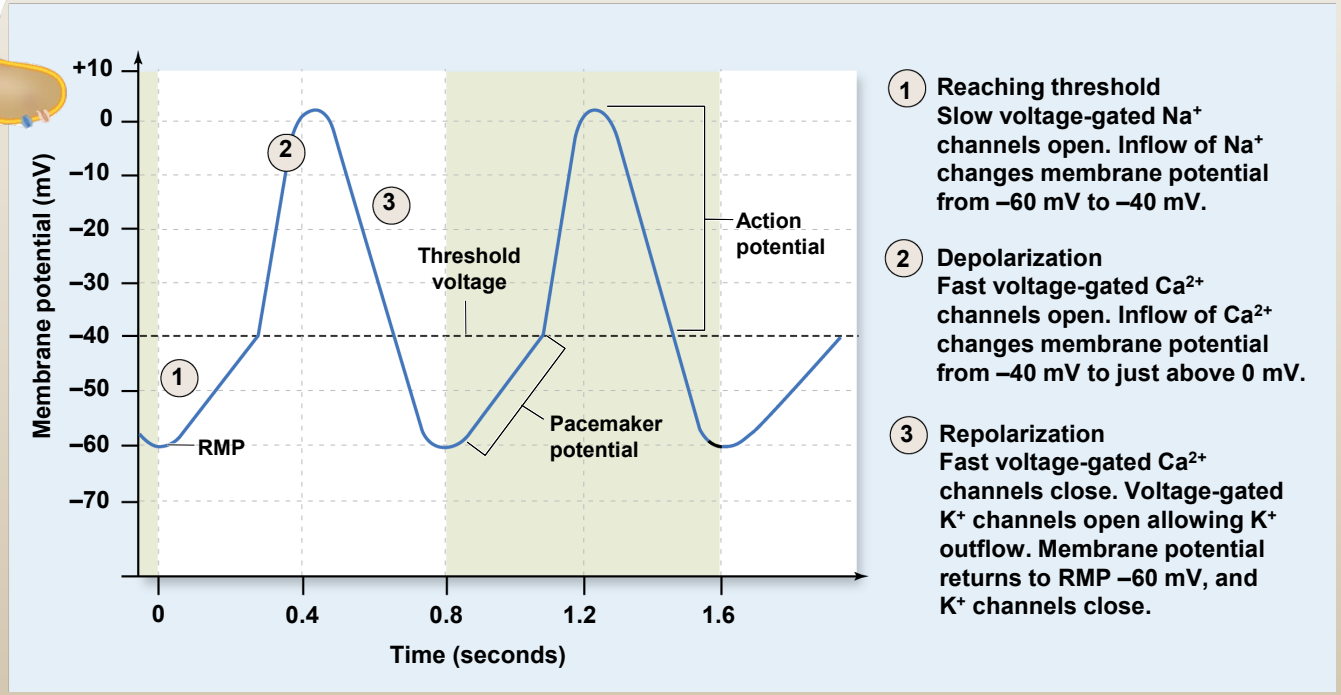


Pacemaker Function



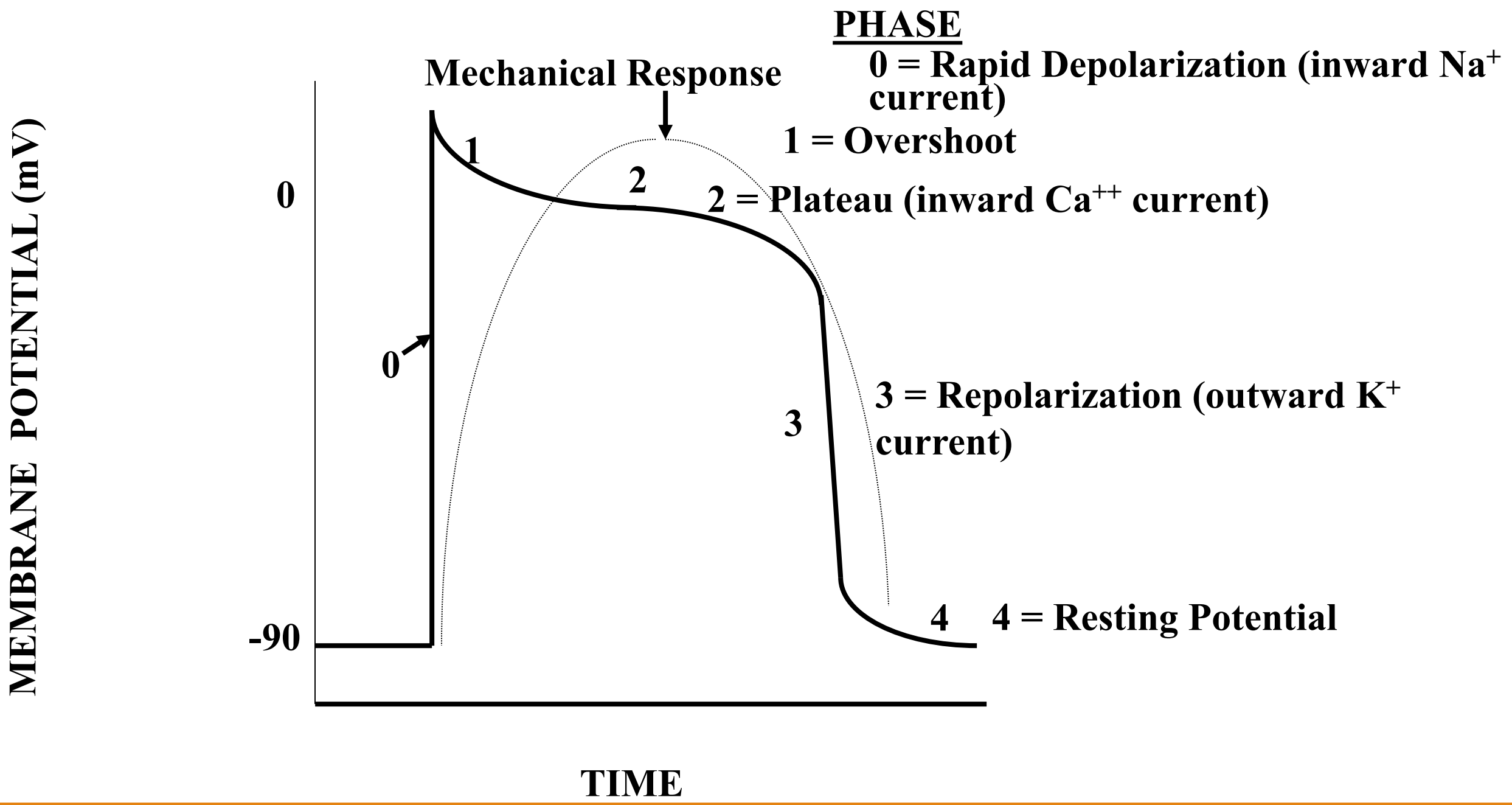


(a)



(b)

1. **Reaching threshold**
   Slow voltage-gated Na^+ channels open. Inflow of Na^+ changes membrane potential from –60 mV to –40 mV.
2. **Depolarization**
   Fast voltage-gated Ca^{2+} channels open. Inflow of Ca^{2+} changes membrane potential from –40 mV to just above 0 mV.
3. **Repolarization**
   Fast voltage-gated Ca^{2+} channels close. Voltage-gated K^+ channels open allowing K^+ outflow. Membrane potential returns to RMP –60 mV, and K^+ channels close.


PHASE
Mechanical Response
0 = Rapid Depolarization (inward Na+ current)
1 = Overshoot
2 = Plateau (inward Ca++ current)
3 = Repolarization (outward K+ current)
4 = Resting Potential
MEMBRANE POTENTIAL (mV)
0
-90
TIME
0
1
2
3
4

Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

Phase 0 = rapid upstroke and depolarization—voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.

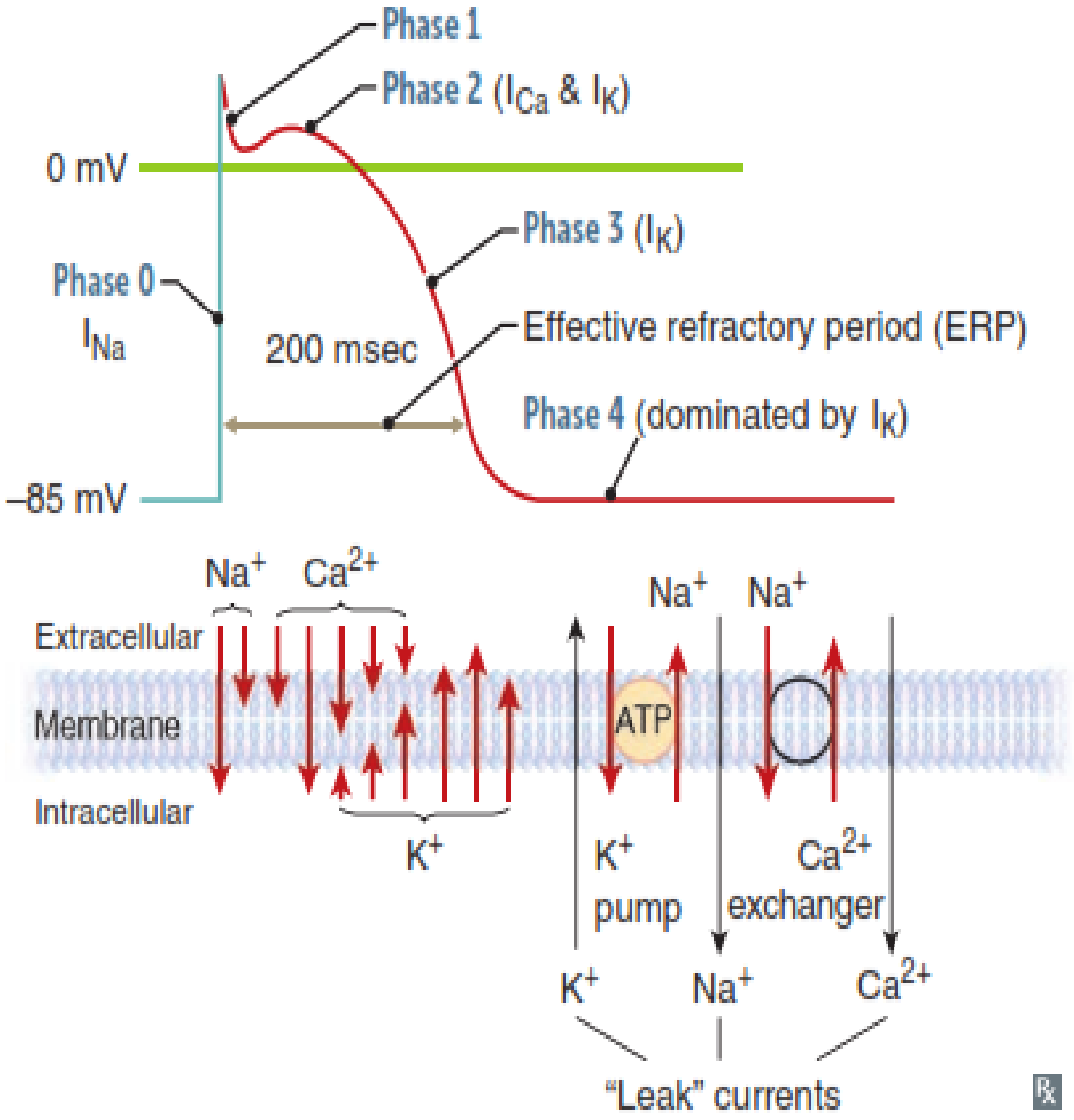
Phase 2 = plateau—Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction.

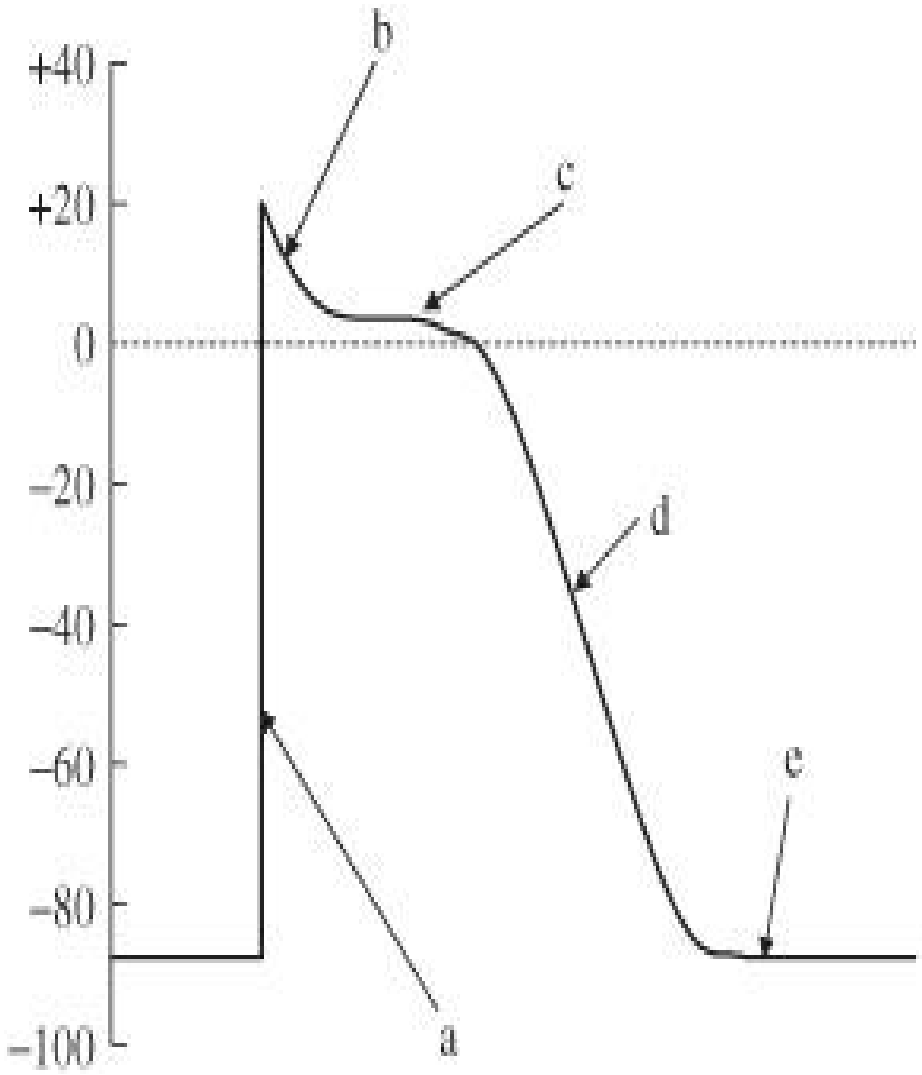
Phase 3 = rapid repolarization—massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx and K^+ efflux.
- Cardiac muscle contraction requires Ca^{2+} influx from ECF to induce Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+}-induced Ca^{2+} release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.





Cardiac action potential.

Describe what happens during each of the following phases of a cardiac action potential:

Phase 0

Upstroke: caused by a rapid transient increase in Na+ conductance, which allows an inward Na+ current to depolarize the membrane (INa)

Phase 1

Brief initial repolarization: caused by a decrease in inward Na+ current due to closure of voltage-activated Na+ channels

Phase 2

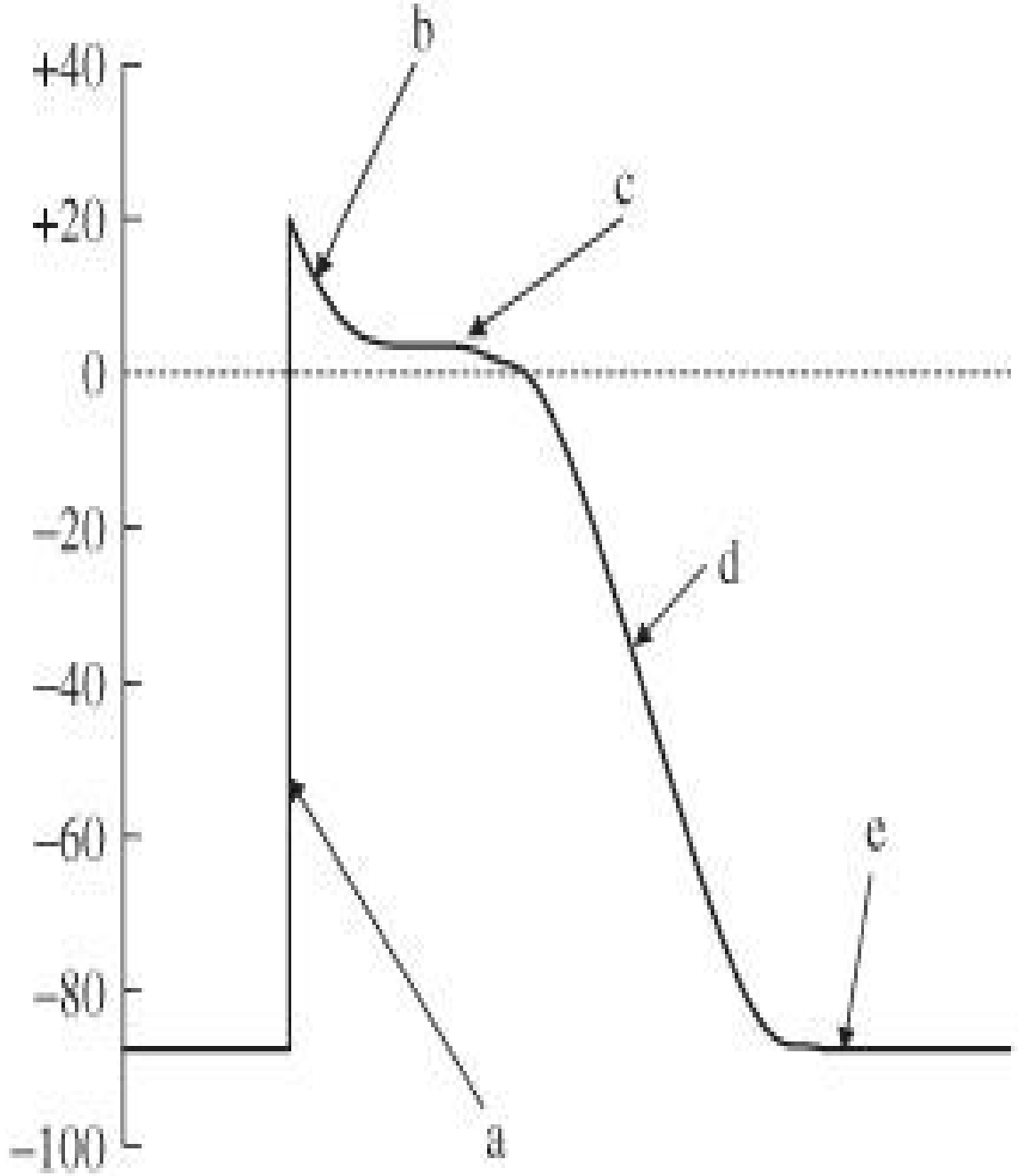
Plateau phase: caused by an increase in Ca2+ conductance and K+ conductance continues to increase; this phase is marked by a net electrical balance between inward Ca+ (ICa) and outward K+ currents (IKout)

Phase 3
Repolarization: K+ conductance peaks. The Ca+ conductance decreases; the electrical balance now favors the large outward K+ current (IKout)

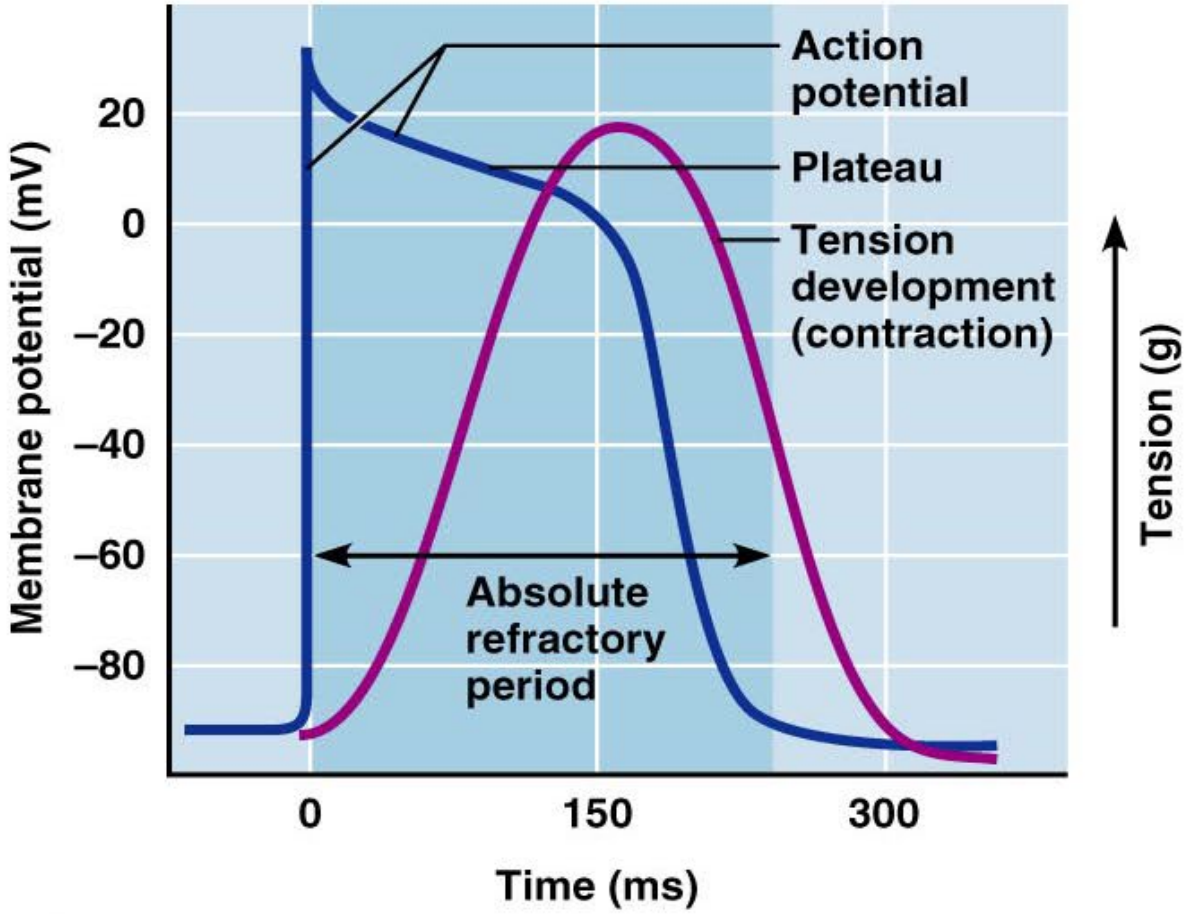
Phase 4
Resting membrane potential: caused by an equilibrium between outward and inward ionic currents

All of these channels are triggered by what?
Threshold; the moment that threshold is reached, the sequence of cardiac conductance is set in motion.

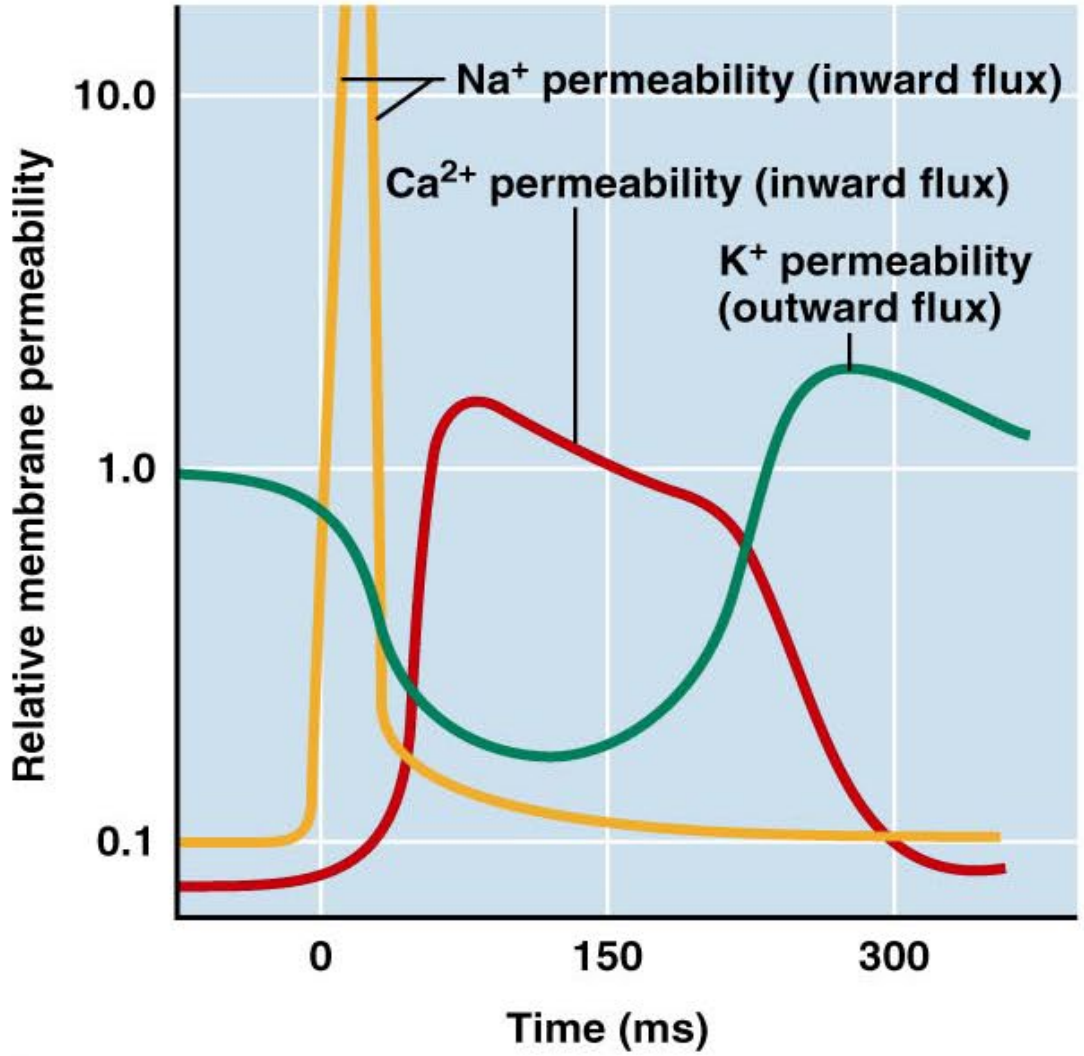
What determines the peak of the cardiac action potential?
Conductance to Na+



Cardiac Membrane Potential

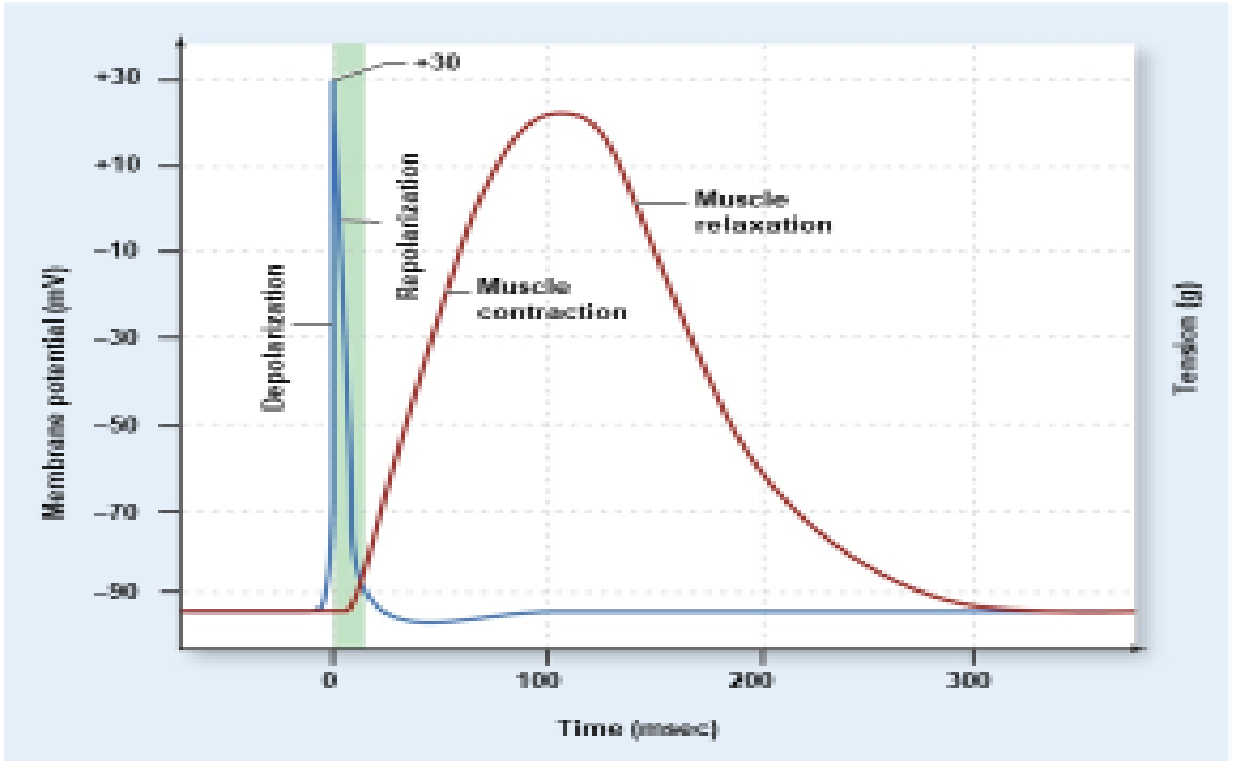


(a)

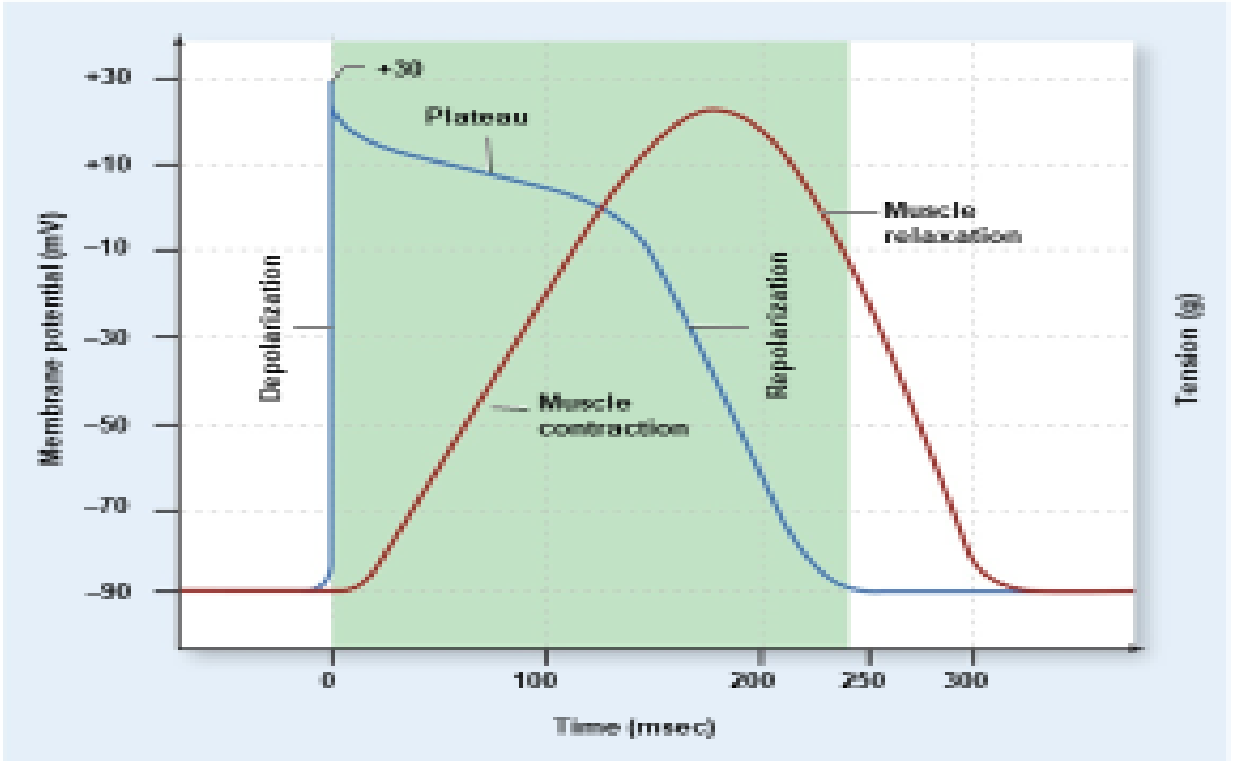


(b)

Fig. 19.19

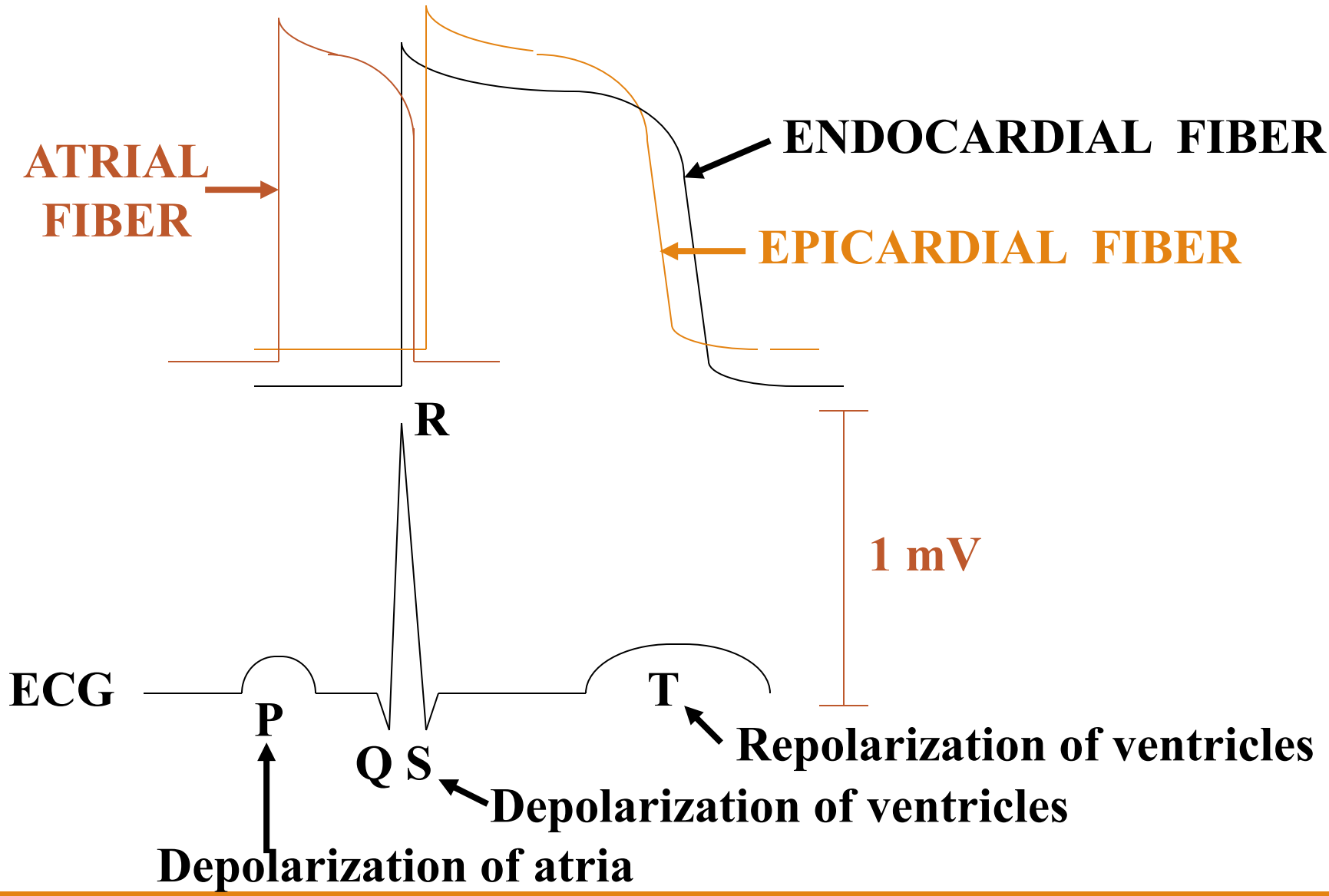


(a) Skeletal muscle

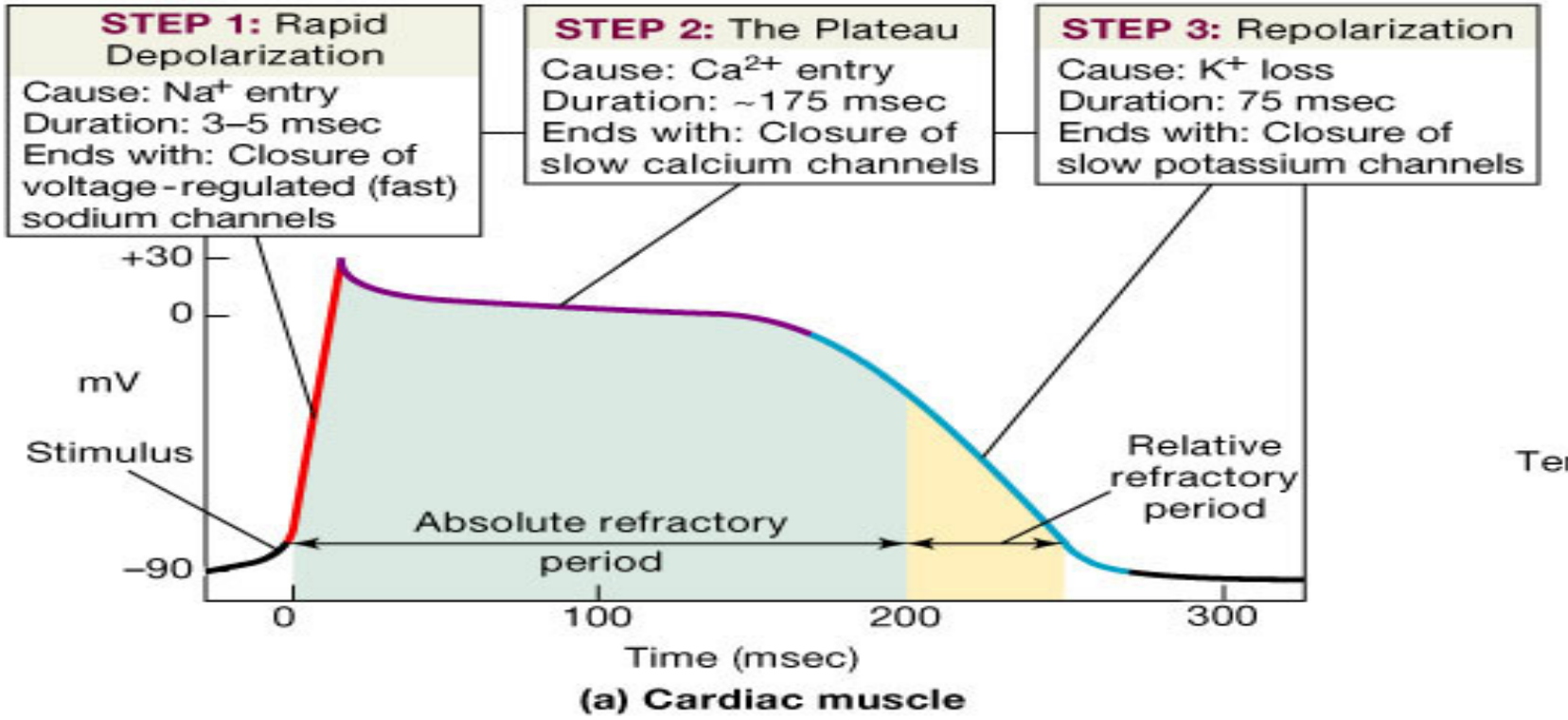


(b) Cardiac muscle

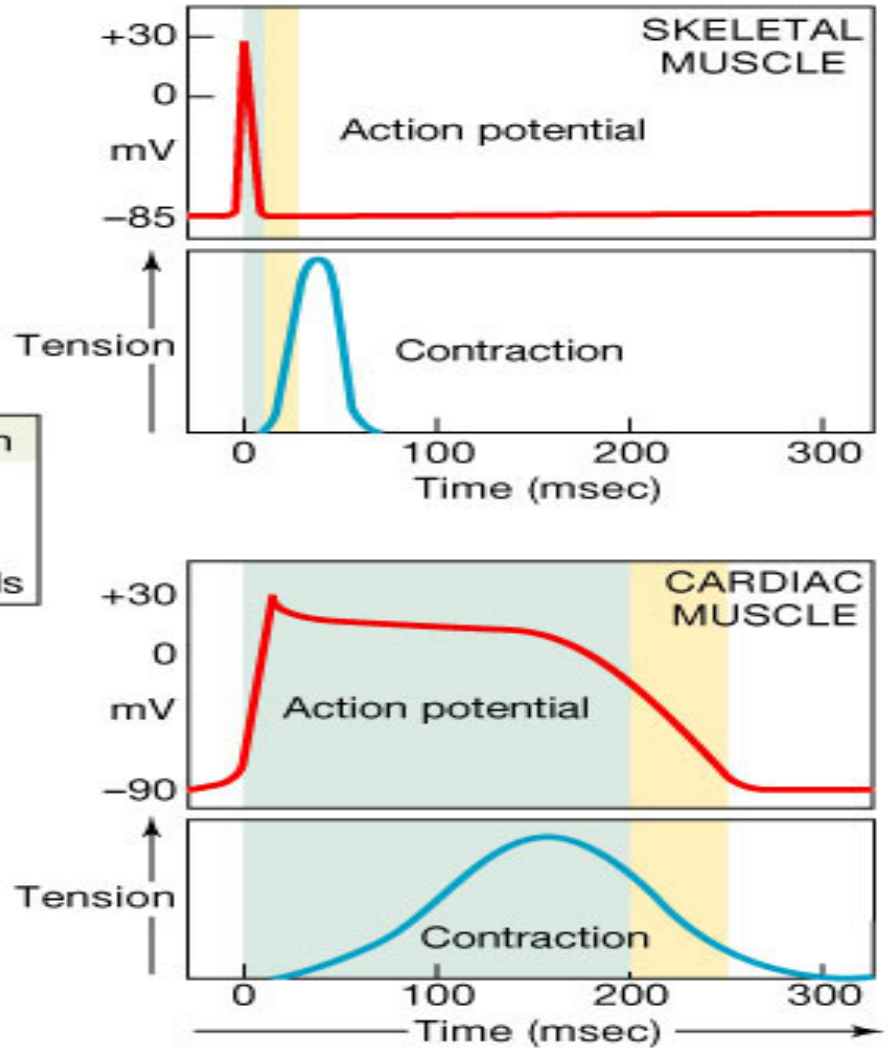
SINGLE VENTRICULAR ACTION POTENTIAL



The Action Potential in Skeletal and Cardiac Muscle



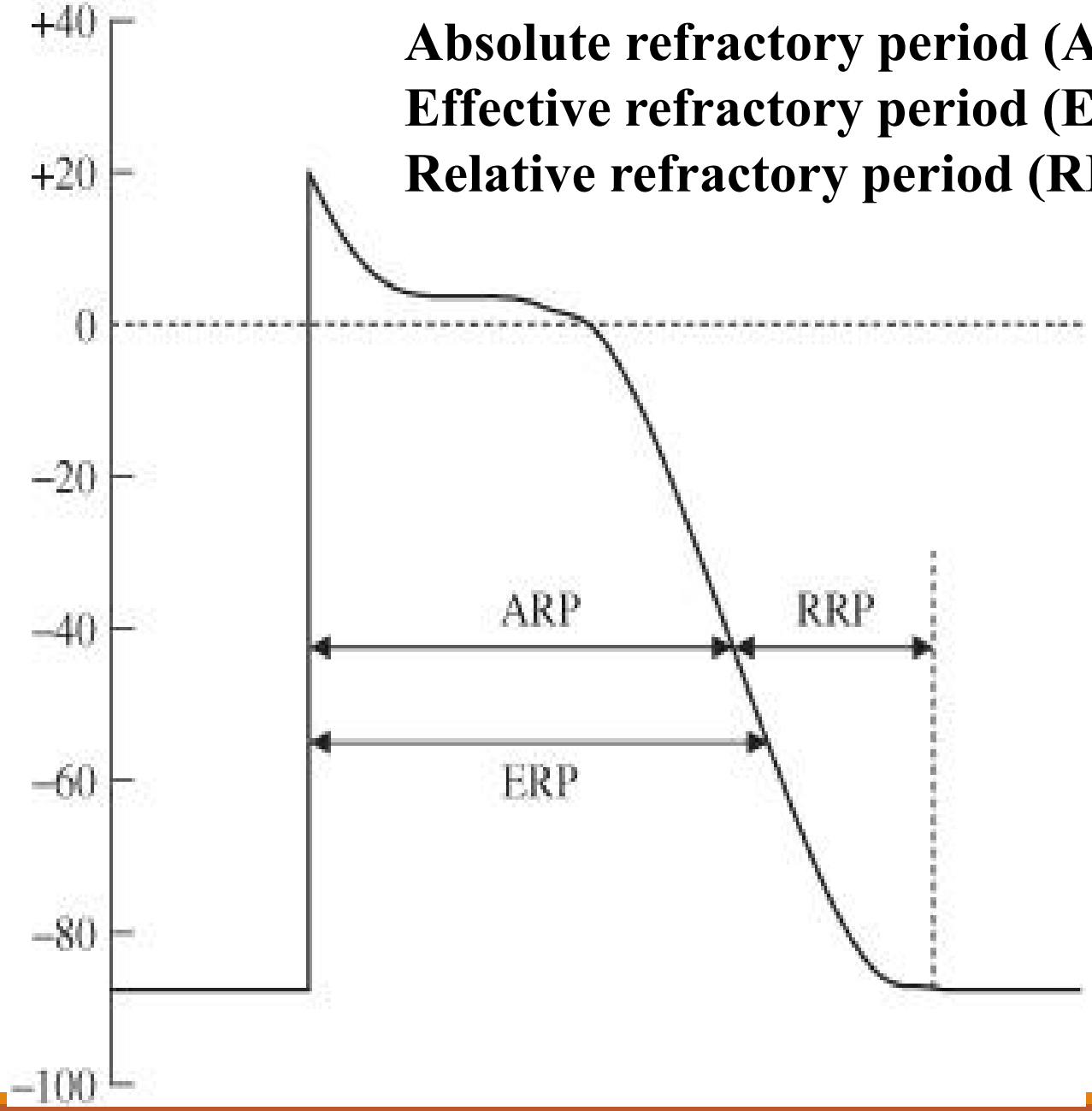
(a) Cardiac muscle



(b)

Figure 20.15

Absolute refractory period (ARP)
Effective refractory period (ERP)
Relative refractory period (RRP)



What is the ARP?
The time during which no number of entering impulses can initiate a new action potential

What is the ERP?
The time during which no conducted action potential can be produced

What is RRP?
The time during which an action potential can be initiated, but requires a larger depolarizing stimulus

Base the heart physiology

- **Automaticity**
- **Excitability**
- **Conductivity**
- **Contractility**

What is cardiac excitability?
The ability of the cardiac muscle cells to conduct an action potential after being depolarized by an inward current

Conductance of what ion determines the resting membrane potential in cardiac muscle cells?
Like all other excitable cells, conductance to K+

What is the resting membrane potential of nonpacemaker cardiac myocytes?
~90 mV, which is close to the K+ equilibrium potential

What maintains the resting membrane potential?
Na+-K+ -ATPase membrane protein

Again, what does it mean when a membrane *depolarizes?*
There is an inward current that brings positive charge into the cell

What does it mean when a membrane *hyperpolarizes* or *repolarizes?*
There is an outward current that removes positive charge from the cell

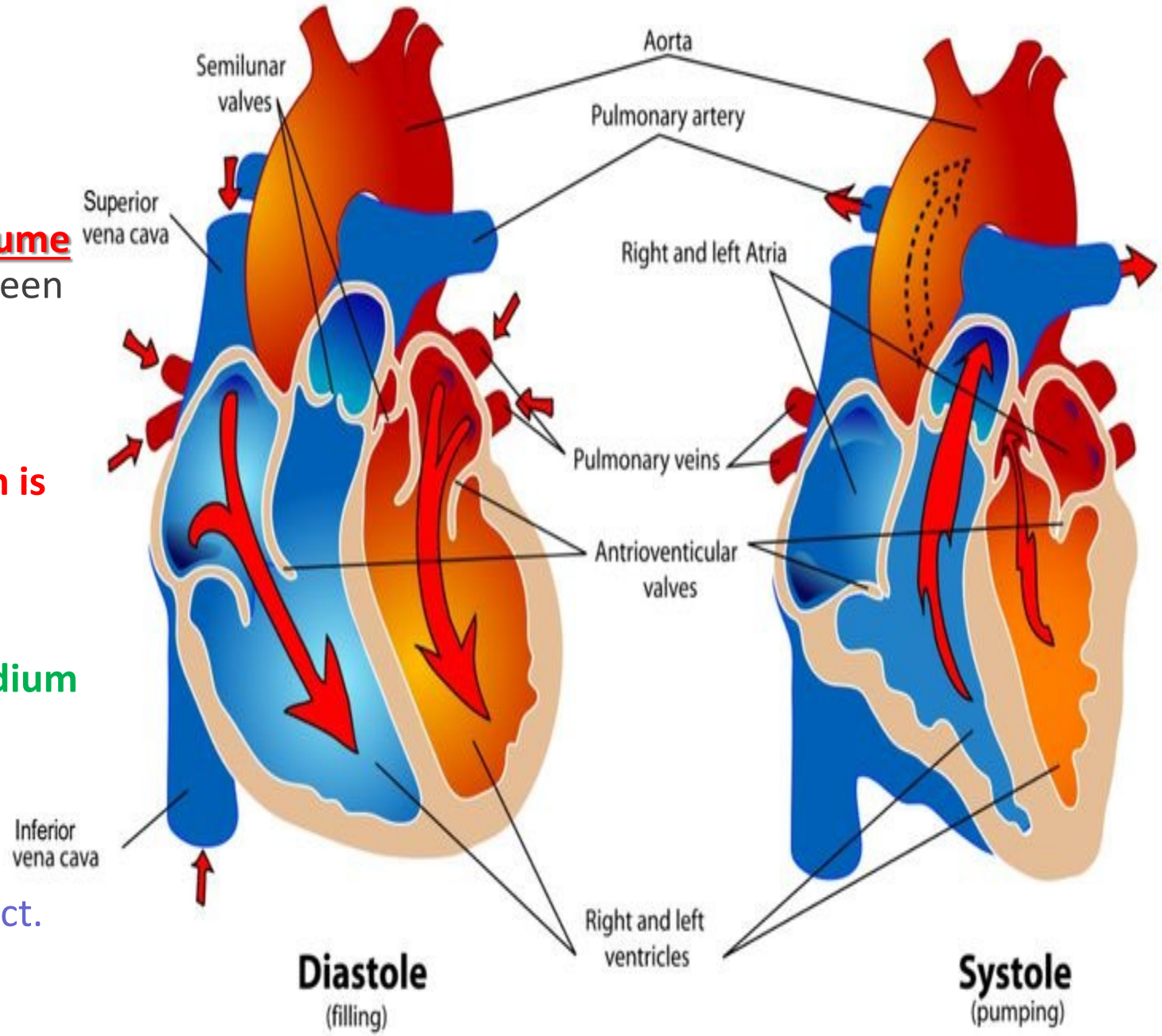
Cardiac Cycle

***Cardiac Cycle*:** the **electrical, pressure and volume changes** that occur in a functional heart between successive heart beats.

- **Phase of the cardiac cycle when myocardium is relaxed is termed *diastole*.**

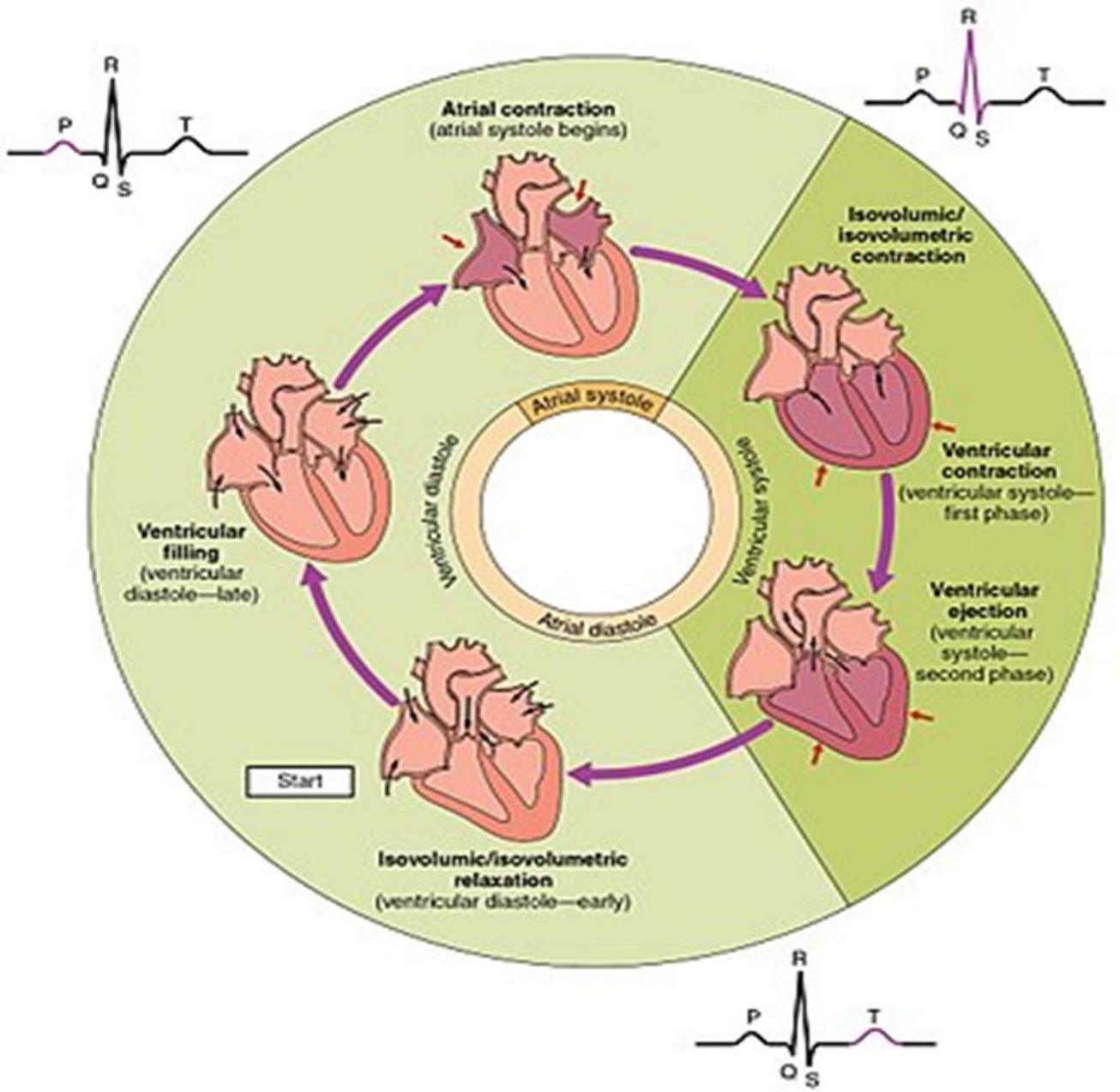
- **Phase of the cardiac cycle when the myocardium contracts is termed *systole*.**

  - ***Atrial systole***: when atria contract.
  - ***Ventricular systole***: when ventricles contract.



Mechanical Events of the Cardiac Cycle

1. **Ventricular Filling Period** [ventricular diastole, atrial systole]
2. **Isovolumetric Contraction Period** [ventricular systole]
3. **Ventricular Ejection Period** [ventricular systole]
4. **Isovolumetric Relaxation Period** [ventricular diastole]



Phases of the Cardiac Cycle

Ventricular filling – mid-to-late diastole

- Heart blood pressure is low as blood enters atria and flows into ventricles
- AV valves are open, then atrial systole occurs

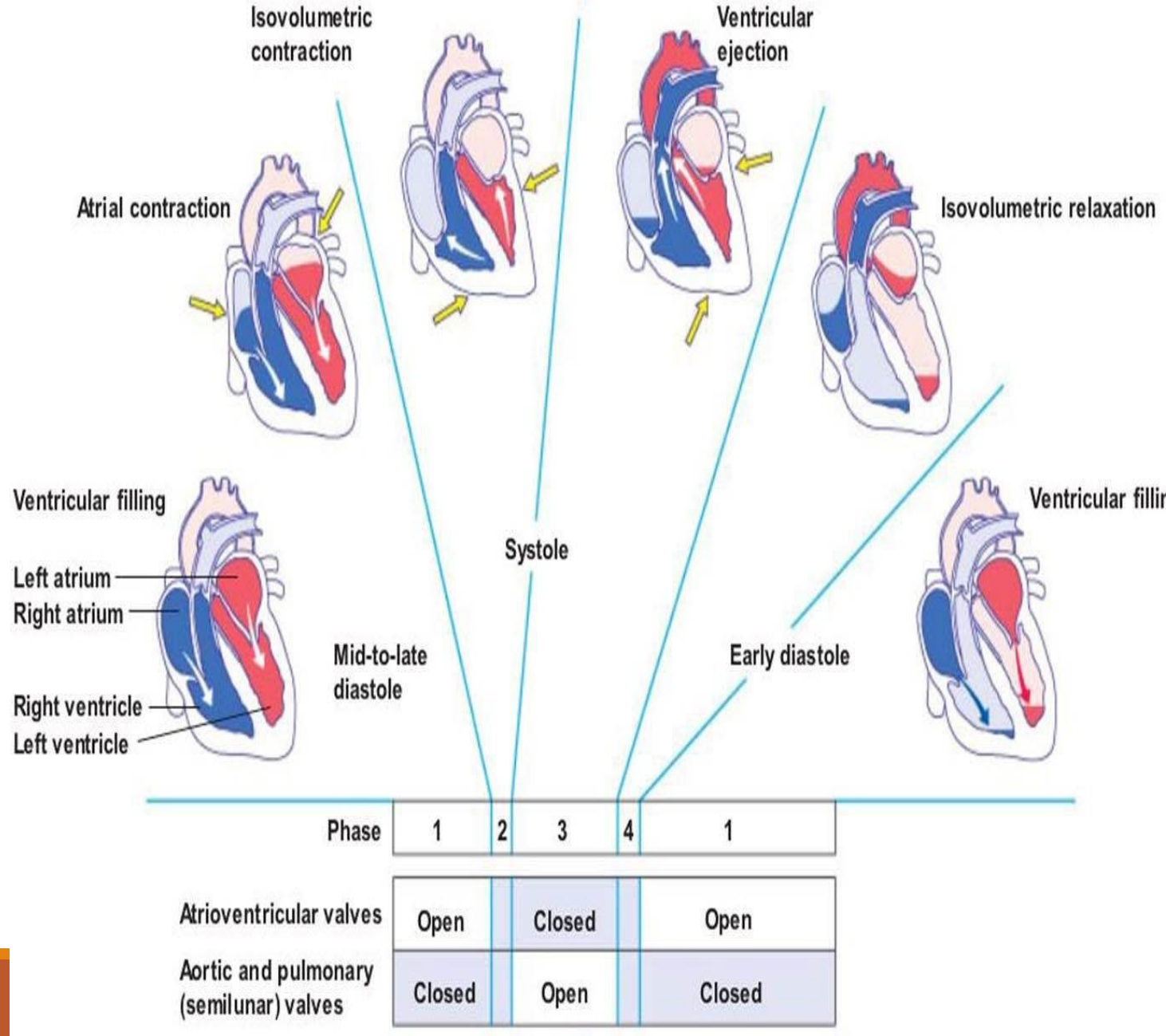
Ventricular systole

- Atria relax
- Rising ventricular pressure results in closing of AV valves
- Isovolumetric contraction phase
- Ventricular ejection phase opens semilunar valves

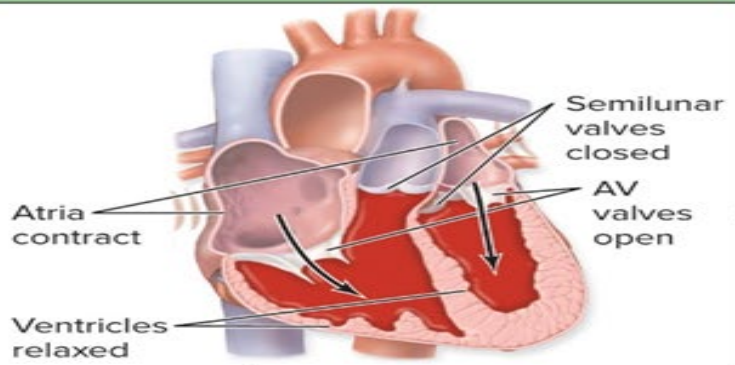
Isovolumetric relaxation – early diastole

- Ventricles relax
- Backflow of blood in aorta and pulmonary trunk closes semilunar valves

Dicrotic notch – brief rise in aortic pressure caused by backflow of blood rebounding off semilunar valves

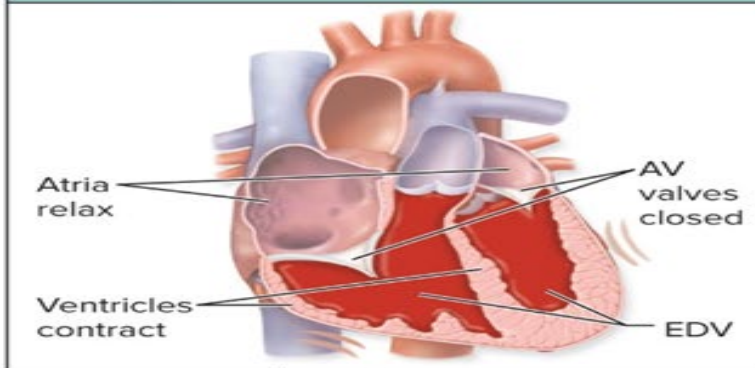


1 Atrial contraction and ventricular filling



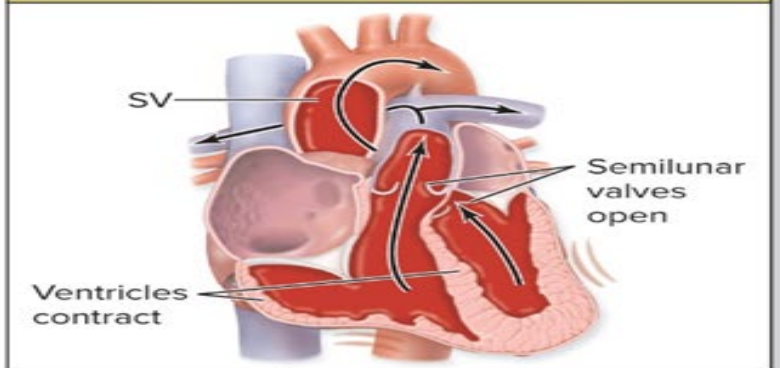
Chambers	Atria contract Ventricles relax
Ventricular pressure	< Atrial pressure < Arterial trunk pressure
Valves	AV valves open Semilunar valves closed

2 Isovolumetric contraction



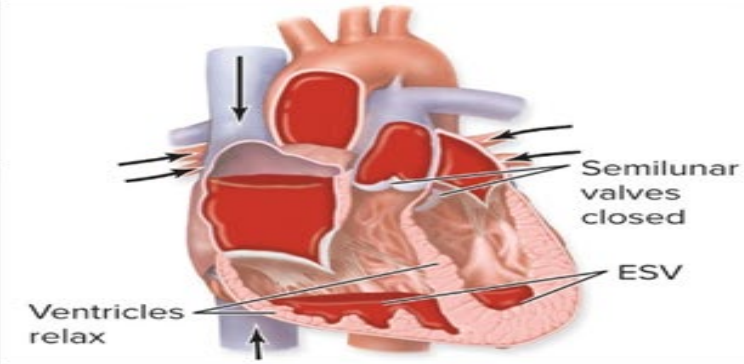
Chambers	Atria relax Ventricles contract
Ventricular pressure	> Atrial pressure < Arterial trunk pressure
Valves	AV valves closed Semilunar valves closed

3 Ventricular ejection



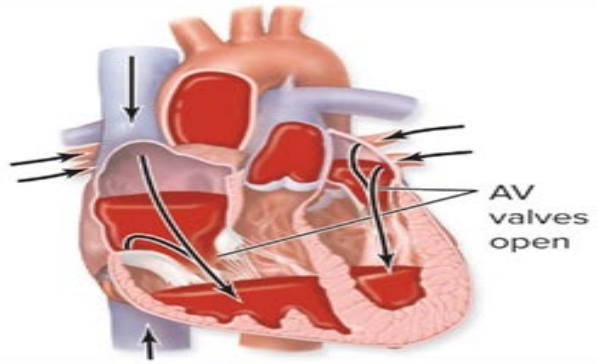
Chambers	Atria relax Ventricles contract
Ventricular pressure	> Atrial pressure > Arterial trunk pressure
Valves	AV valves closed Semilunar valves open

4 Isovolumetric relaxation



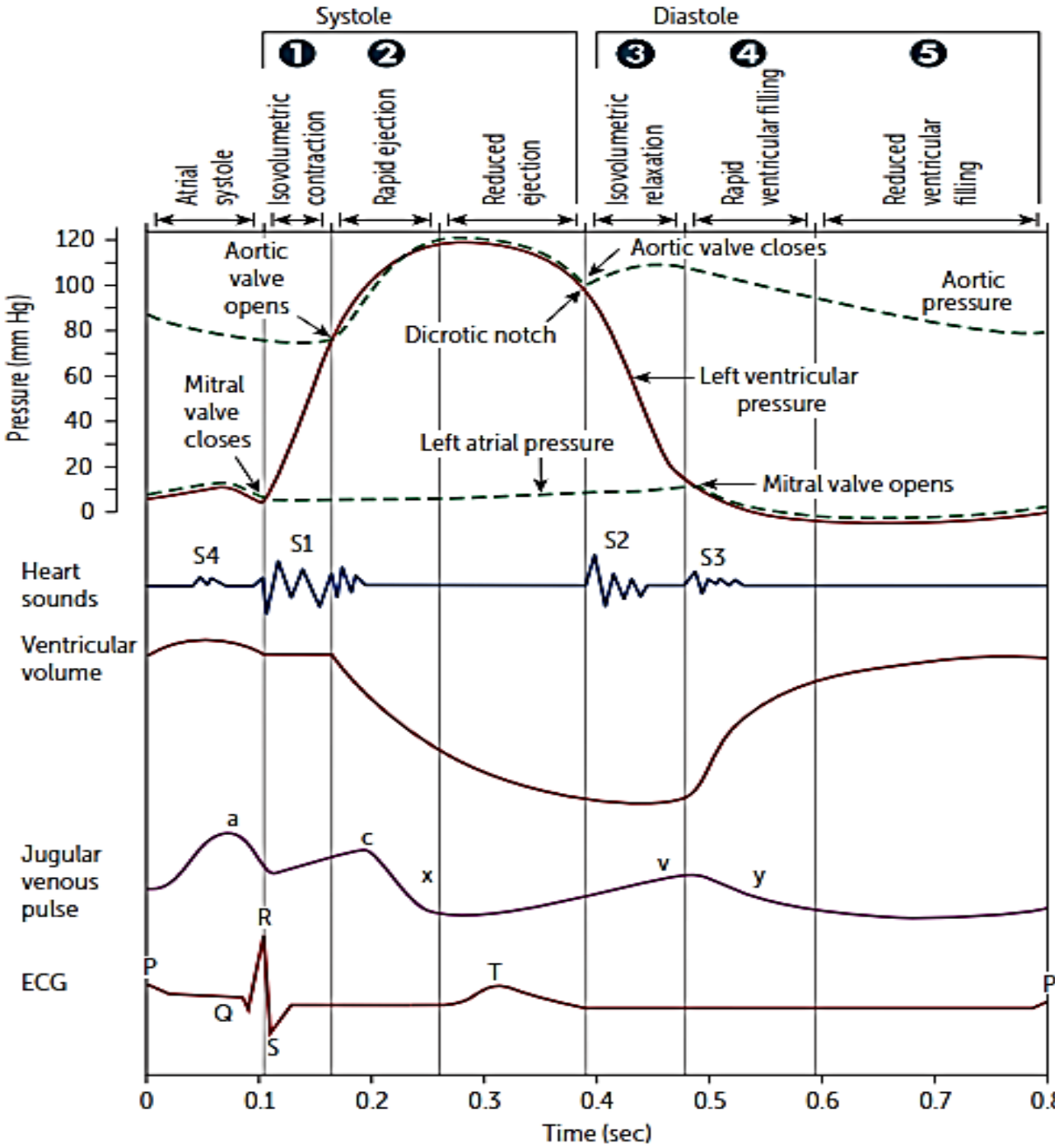
Chambers	Atria relax Ventricles relax
Ventricular pressure	> Atrial pressure < Arterial trunk pressure
Valves	AV valves closed Semilunar valves closed

5 Atrial relaxation and ventricular filling



Chambers	Atria relax Ventricles relax
Ventricular pressure	< Atrial pressure < Arterial trunk pressure
Valves	AV valves open Semilunar valves closed

SV: Stroke volume
EDV: End-diastolic volume
ESV: End-systolic volume



Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure.Loudest at left upper sternal border.

S3—in early diastole during rapid ventricular filling phase. Associated with filling pressures (eg, mitral regurgitation, HF) and more common in dilated ventricles (but can be normal in children, young adults, and pregnant women).

S4—in late diastole ("atrial kick"). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with
ventricular noncompliance (eg, hypertrophy).

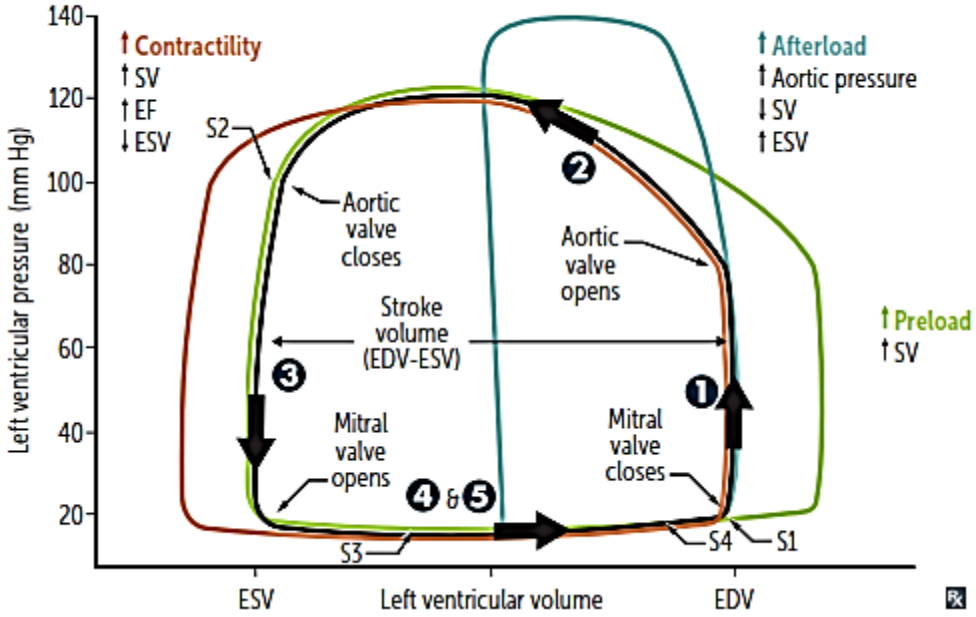
Left atrium must push against stiff LV wall.
Consider abnormal, regardless of patient age.

Jugular venous pulse (JVP):

- **a wave—atrial contraction. Absent in atrial**
- fibrillation (AF).
- **c wave—RV contraction (closed tricuspid valve**
- bulging into atrium).
- x descent—downward displacement of closed
- tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.
- **v wave—right atrial pressure due to filling ("villing") against closed tricuspid valve.**
- **y descent—RA emptying into RV. Prominent**

in constrictive pericarditis, absent in cardiac tamponade.

Pressure-volume loops and cardiac cycle



The black loop represents normal cardiac physiology.

Phases—left ventricle:

❶ Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O_2 consumption

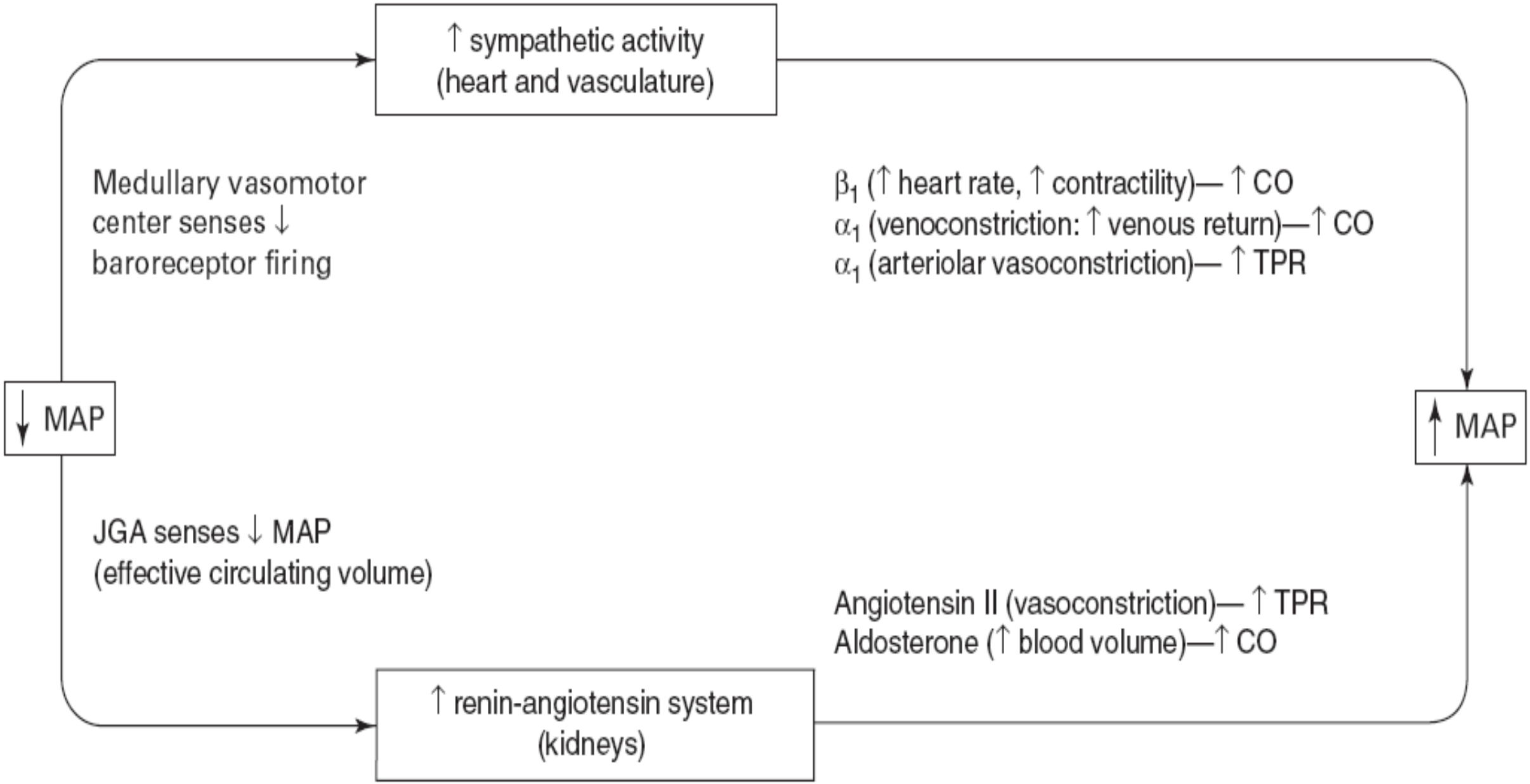
❷ Systolic ejection—period between aortic valve opening and closing

❸ Isovolumetric relaxation—period between aortic valve closing and mitral valve opening

❹ Rapid filling—period just after mitral valve opening

❺ Reduced filling—period just before mitral valve closing

Control of mean arterial pressure



What is Cardiac Index ?

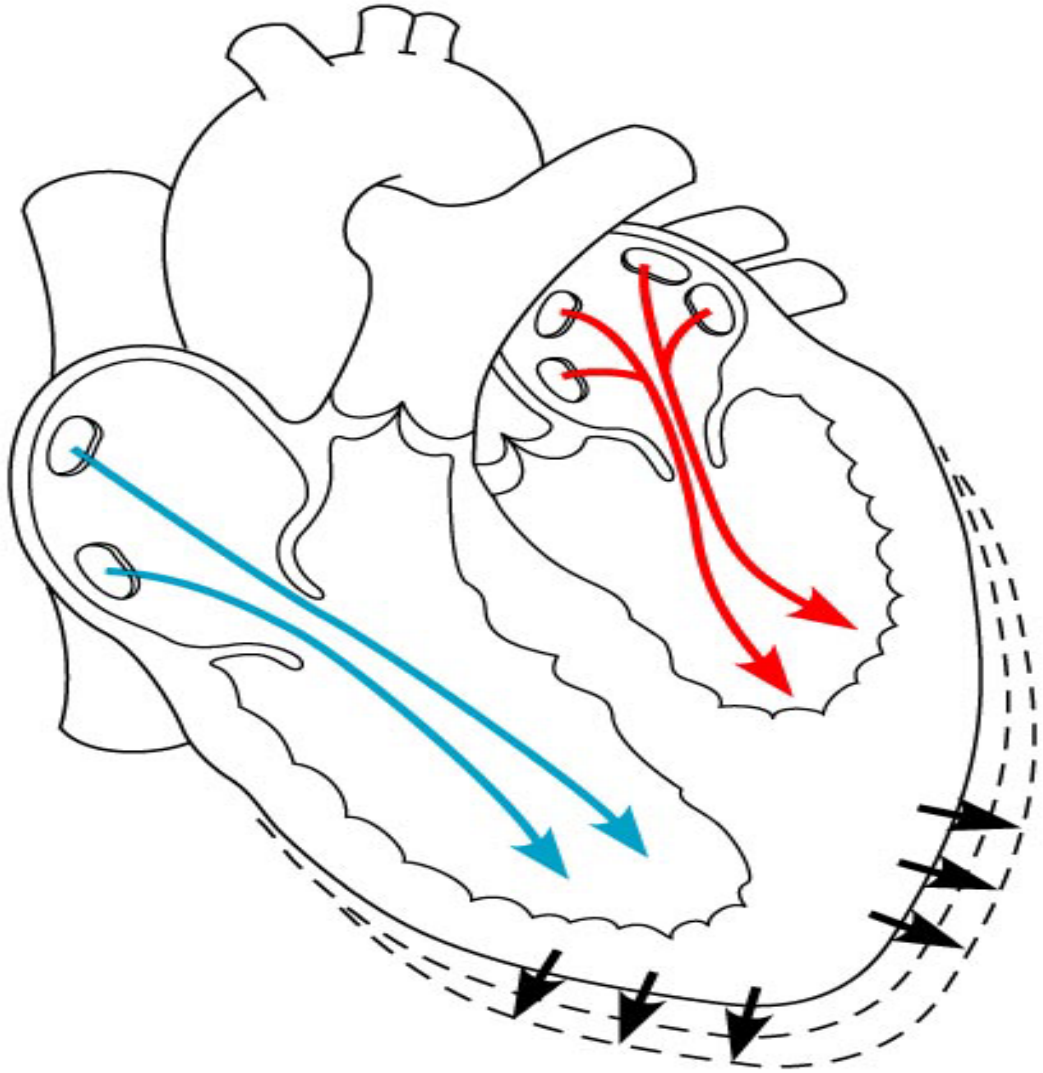
It is cardiac output per minute per square meter of body surface area.

Normal Cardiac Index = 3.2 Liter /min/ sq meter body surface area.

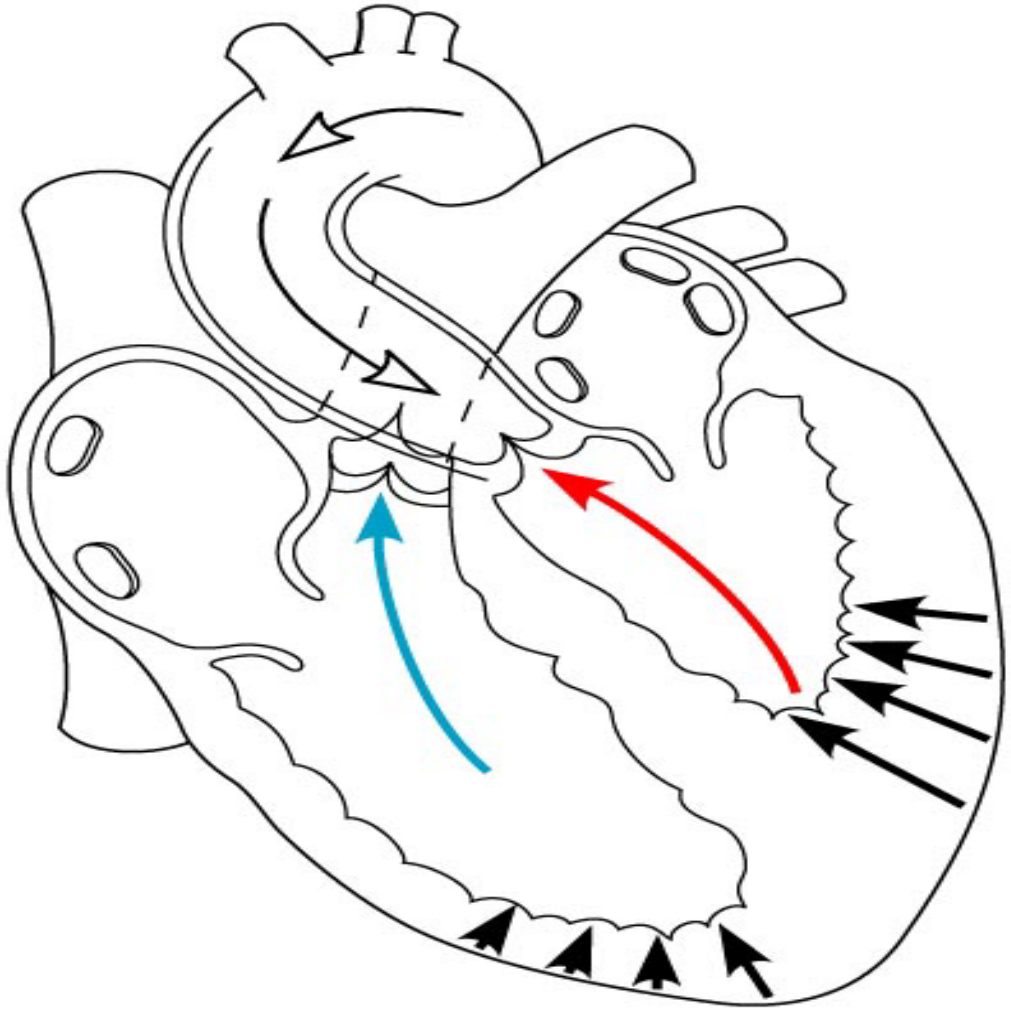
What is Cardiac Reserve ?

It is the difference between cardiac output at rest and maximum volume of blood that heart can pump per minute.

Preload and Afterload



(a) Preload



(b) Afterload

Ejection fraction (EF) is the percentage of ventricular end diastolic volume (EDV) which is ejected with each stroke.

$$EF = \frac{SV\ (EDV - ESV)}{EDV} \times 100$$

$$\frac{75}{120} \times 100 = 62.5\%$$

- **Normal ejection fraction is about 60 – 65 %.**
- **Ejection fraction is good index of ventricular function.**

Cardiac output (CO)

= 5 L

Cardiac output (CO) = (stroke volume) × (heart rate).

Fick principle:

$$CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}$$

$$\text{Mean arterial pressure} = \begin{pmatrix}\text{cardiac}\\ \text{output}\end{pmatrix} \times \begin{pmatrix}\text{total peripheral}\\ \text{resistance}\end{pmatrix}$$

MAP = ⅔ diastolic pressure + ⅓ systolic pressure.

Pulse pressure = systolic pressure – diastolic pressure.

Pulse pressure is proportion to stroke volume.

$$SV = \frac{CO}{HR} = EDV - ESV$$

During exercise, CO ↑ initially as a result of an ↑ in SV. After prolonged exercise, CO ↑ as a result of an ↑ in HR.

If HR is too high, diastolic filling is incomplete and CO ↓ (e.g., ventricular tachycardia).

Cardiac Output (CO) and Reserve

❖CO is the amount of blood pumped by each ventricle in one minute

CO is the product of heart rate (HR) and stroke volume (SV)➔Stroke volume is determined by three factors:

Preload

Afterload

Contractility

❖HR is the number of heart beats per minute

❖SV is the amount of blood pumped out by a ventricle with each beat

❖Cardiac reserve is the difference between resting and maximal CO

SV is the amount of blood pumped out by a ventricle with each beat

- **SV = EDV - ESV**
- **EDV = amount of blood collected in a ventricle during diastole** It is about 120 – 130 ml.
- **ESV = amount of blood remaining in a ventricle after contraction.** It is about 50 to 60 ml

Ejection Fraction (EF) = Stroke Volume / End Diastolic Volume

Example of Cardiac Output

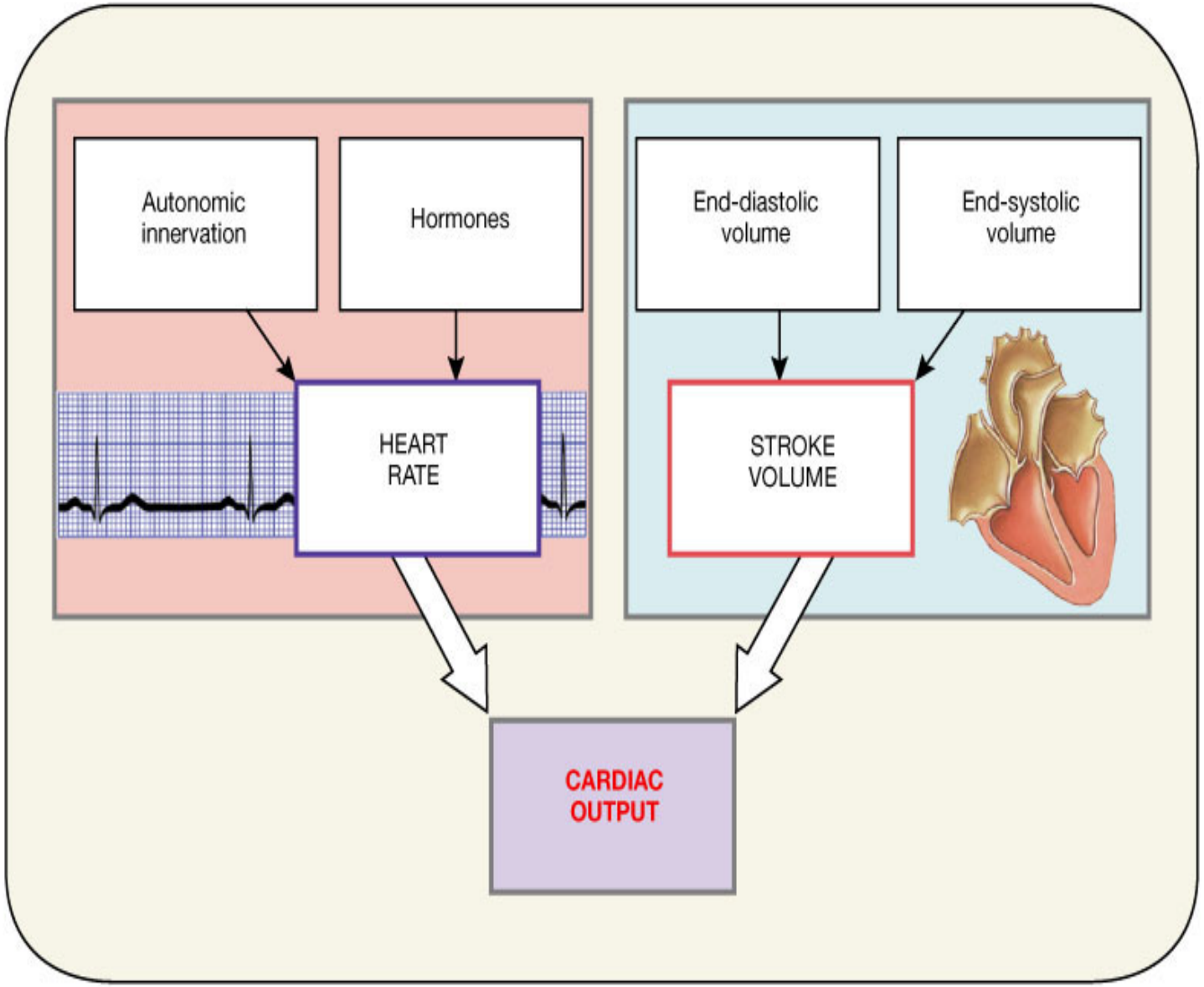
- **CO (ml/min) = HR (75 beats/min) x SV (70 ml/beat)**
- **CO = _____**

CO increases during exercise, and depending on exercise, it can increase to **20–25 liters/min [up to 35 liters/min is recorded in trained athlete during heavy exercise].**

➢**How ?**

- By increasing stroke volume and heart rate.

Factors Affecting Cardiac Output



Stroke volume can be increased by TWO mechanism:

1. INTRINSIC CONTROL – **by increasing venous return to the heart**

2. EXTRINSIC CONTROL – **due to the sympathetic stimulation of the heart**

Figure 20.20

Effect of Autonomic Nervous System on Heart

Area Affected	Effect of Parasympathetic Stimulation	Effect of Sympathetic Stimulation
SA Node	Decreases the rate of depolarization to threshold; decreases the heart rate	Increases the rate of depolarization to threshold; increases the heart rate
AV Node	Decreases excitability; increases the AV nodal delay	Increases excitability; decreases the AV nodal delay
Ventricular Conduction Pathway	No effect	Increases excitability; hastens conduction through the bundle of His and Purkinje cells
Atrial Muscle	Decreases contractility; weakens contraction	Increases contractility; strengthens contraction
Ventricular Muscle	No effect	Increases contractility; strengthens contraction

SYMPATHETIC : It regulates the action potential frequency of the SA node.

- ❑Regulates vasoconstriction.
- ❑Regulates venomotor tone.
- ❑Stimulate the secretion of epinephrine and renin.

Factors Affecting Stroke Output

Preload - amount ventricles are stretched by contained blood

Contractility - cardiac cell contractile force due to factors other than EDV

- Increase in contractility comes from:
  - Increased sympathetic stimuli
  - Certain hormones
  - Ca2+ and some drugs
- **Agents/factors that decrease contractility:**
  - Acidosis
  - Increased extracellular K+
  - Calcium channel blockers

SV = end diastolic volume (EDV) minus end systolic volume (ESV)
EDV = amount of blood collected in a ventricle during diastole
ESV = amount of blood remaining in a ventricle after contraction

Afterload -back pressure exerted by blood in the large arteries leaving the heart

Frank-Starling Law of the Heart

- Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical factor controlling stroke volume
- Slow heartbeat and exercise increase venous return to the heart, increasing SV

Frank-Starling Law of the Heart

Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical **factor controlling stroke volume;**

↑EDV leads to ↑stretch of myocardial .

- **↑preload → ↑stretch of muscle → ↑force of contraction →↑SV**
- Unlike skeletal fibers, cardiac fibers contract MORE FORCEFULLY when stretched thus ejecting MORE BLOOD (↑SV)
- **If SV is increased, then ESV is decreased!!**

Slow heartbeat and exercise increase venous return (VR) to the heart, increasing SV

- VR changes in response to blood volume, skeletal muscle activity, alterations in cardiac output
- **↑VR → ↑EDV and ↓in VR → ↓ in EDV**
- **Any ↓ in EDV → ↓ in SV**

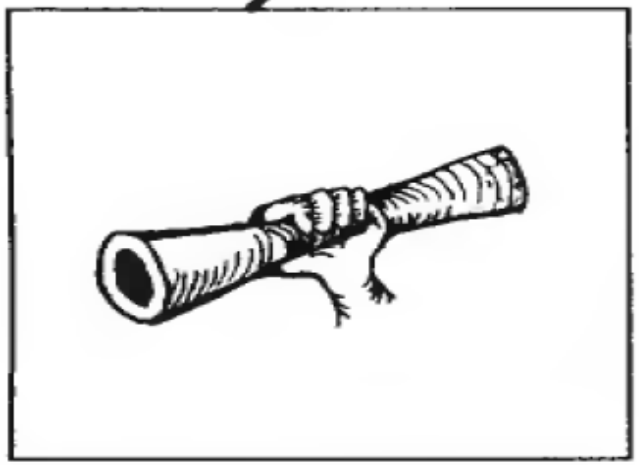
Blood loss and extremely rapid heartbeat decrease SV

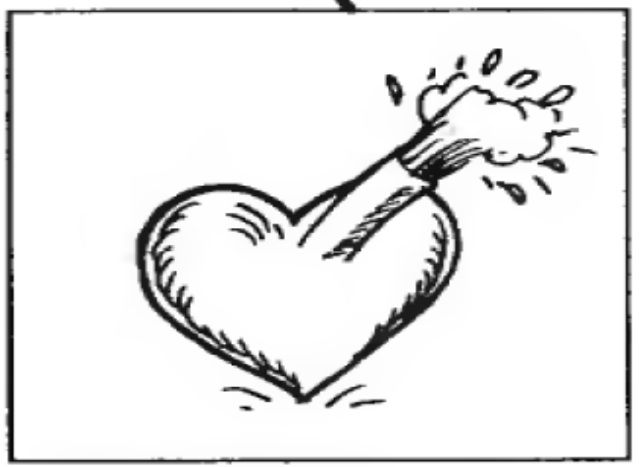
Mechanism of Cardiac Length – Tension Relationship

❖When there is increase in the length of cardiac muscle fiber to the optimal length, there is **maximum sliding of actin and myosin and we get maximum contraction**.

- Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical factor controlling stroke volume
- **Slow heartbeat and exercise increase venous return to the heart, increasing SV**
- **Blood loss and extremely rapid heartbeat decrease SV**

BLOOD PRESSURE





↑PERIPHERAL RESISTANCE

- ↑Vasoconstriction
  - ↑ADH
  - ↑Renin/Angiotensin/Aldosterone
  - ↑Sympathetic stimulation of
    - α1 receptors (blood vessels)
    - β1 receptors (kidney glomerular cells)
  - Autoregulatory mechanisms
  - ↑Vascular reactivity
  - ↓Nitric oxide
- ↑Blood viscosity
- ↓Blood vessel elasticity

↑CARDIAC OUTPUT

- ↑Blood volume
  - ↑Sodium intake
    - Osmotic effect on water retention
    - ↑Osmolality causes thirst
    - ↑Osmolality stimulates ADH secretion
  - ↑Aldosterone
  - ↓ANF
  - ↑ADH
  - ↑Water intake
  - ↓Water output
- ↑Sympathetic stimulation
- ↓Parasympathetic stimulation
- Starling's Law

- **Blood pressure is the force exerted on a blood vessel wall by the blood.**
- **Blood must circulate through the body and organs to maintain life**
- **The Heart is the pump that circulates the blood**
- **Pressure difference in the vascular system ensures that blood flows around the body**

LOCATION AND EFFECTS OF STIMULATION OF ADRENERGIC RECEPTORS

ALPHA-1 RECEPTORS

Arterioles and Veins:
constriction (epinephrine and norepinephrine)

Glands:
↓ secretions

Eye:
constriction of radial muscle

Intestine:
↓ motility

ALPHA-2 RECEPTORS

CNS Postsynaptic Terminals:
↓ sympathetic outflow from brain

CNS Presynaptic Terminals:
norepinephrine release

Beta Islet Cells of Pancreas:
↓ secretion

BETA-1 RECEPTORS

Heart:
↑ heart rate (SA node)
↑ contractility
↑ conduction velocity
↑ automaticity

Kidney:
↑ renin secretion

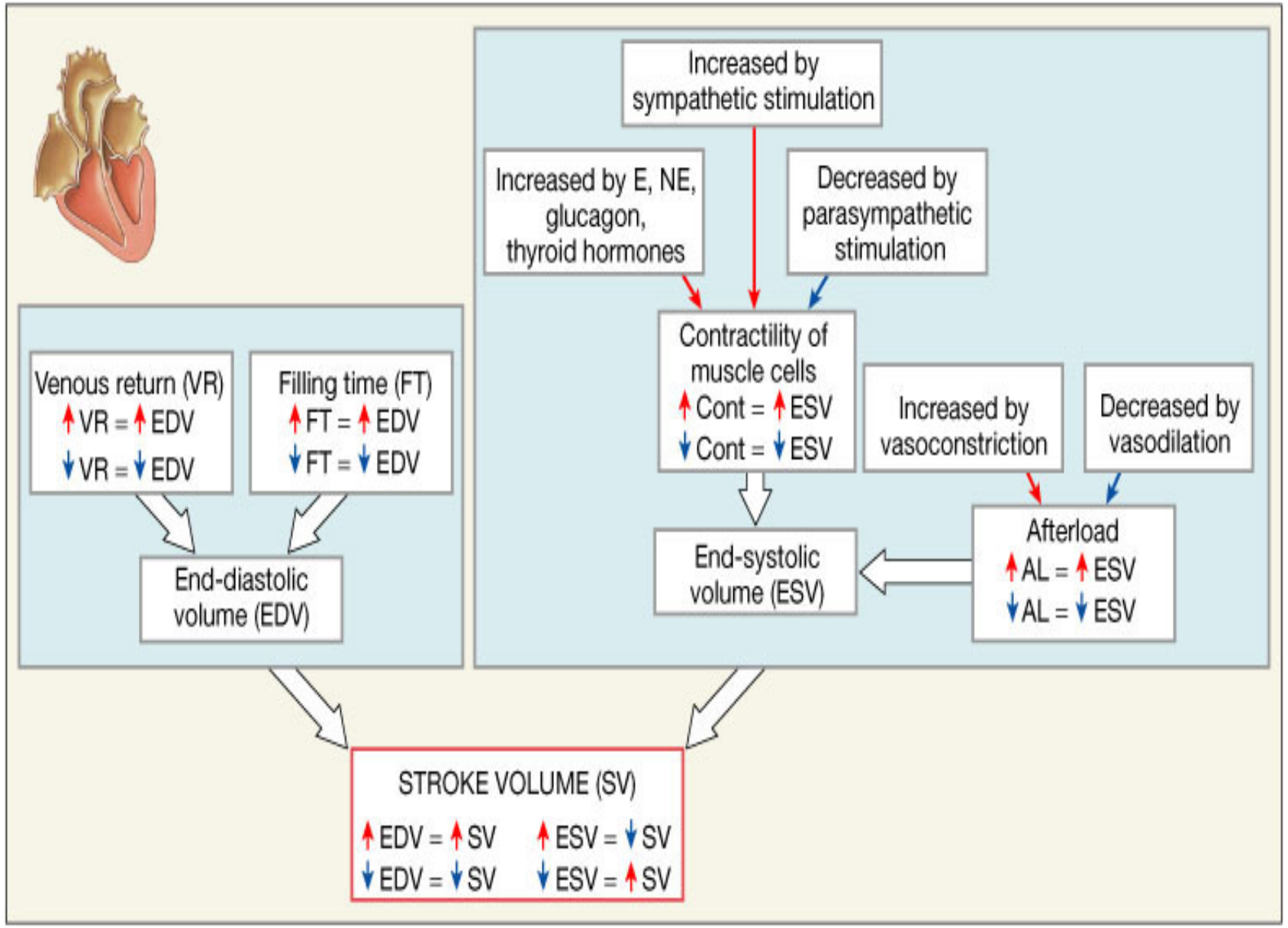
BETA-2 RECEPTORS

Trachea and Bronchioles:
dilation

Pregnant/nonpregnant Uterus:
relaxation

Arterioles (no beta-2 receptors in skin or brain):
dilation (epinephrine)

Factors Affecting Stroke Volume

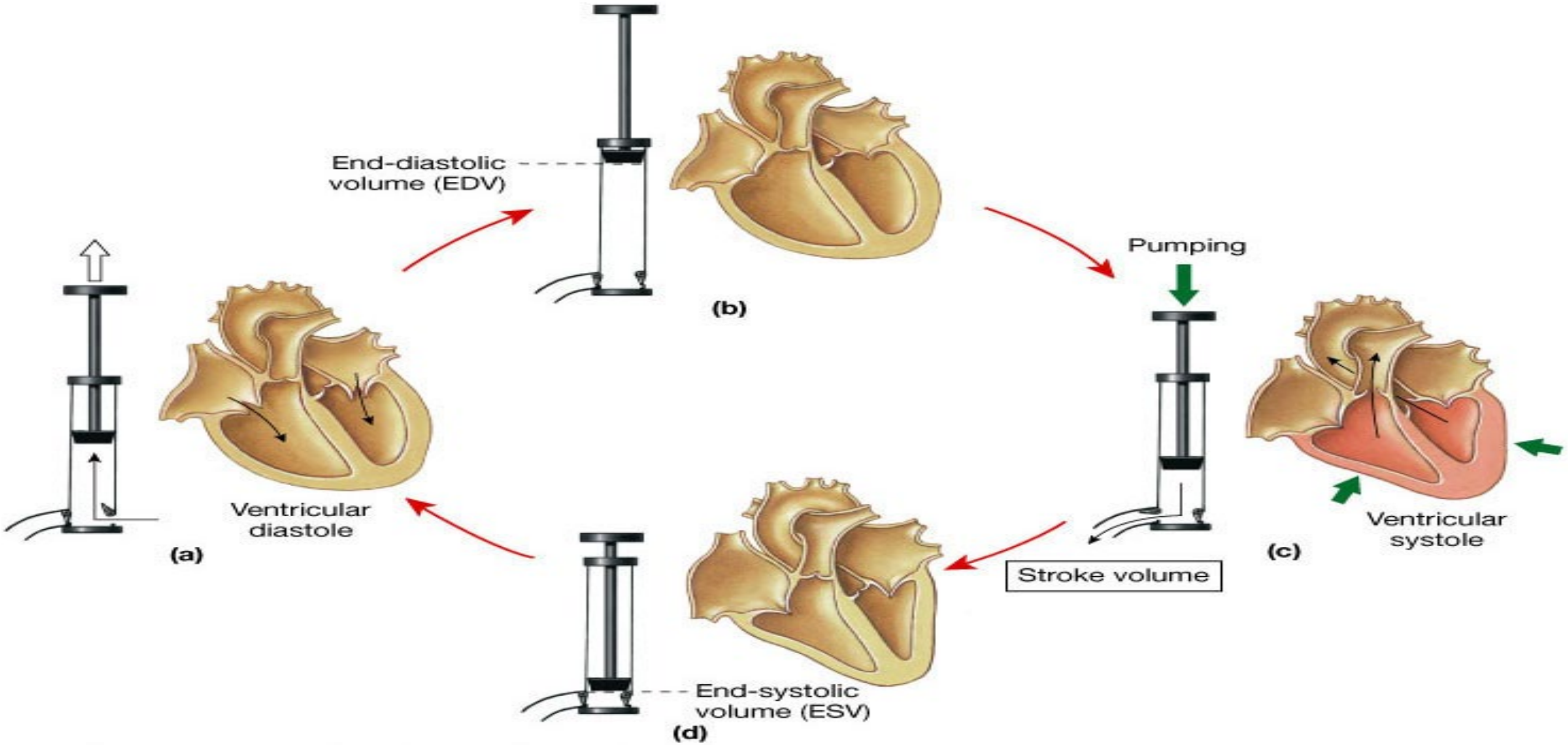


Preload – amount ventricles are stretched by contained blood

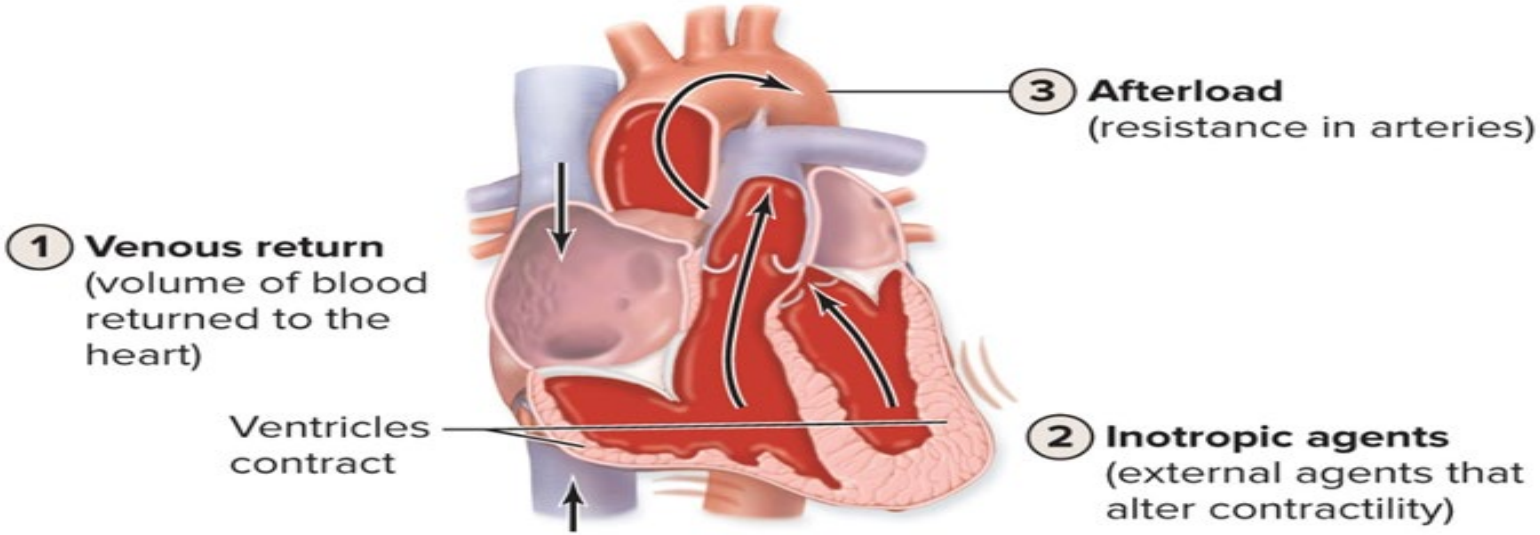
Contractility – cardiac cell contractile force due to factors other than EDV

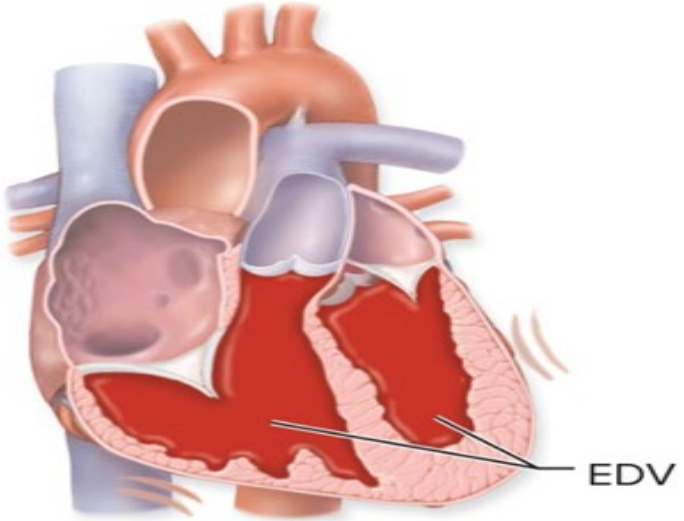
Afterload – back pressure exerted by blood in the large arteries leaving the heart

A Simple Model of Stroke Volume

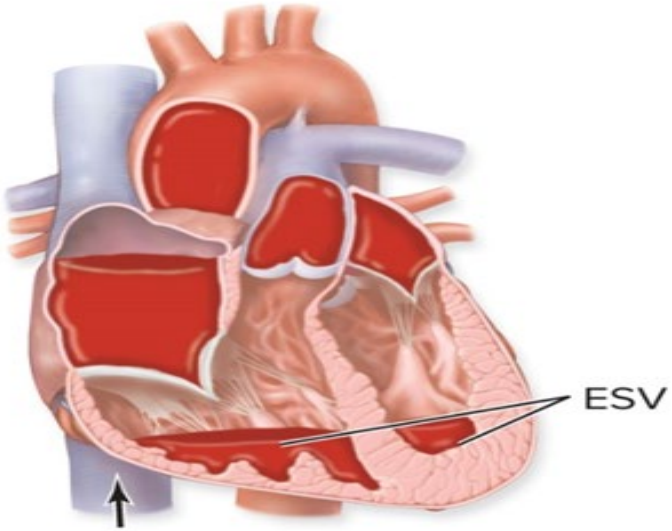


Stroke volume (volume of blood ejected per heartbeat)





End-diastolic volume (EDV)



End-systolic volume (ESV)

EDV − SV = ESV
130 mL − 70 mL = 60 mL

Cardiac output variables

Stroke Volume affected by Contractility, Afterload, and Preload. ↑ SV when ↑ preload, ↓ afterload, or ↑ contractility.

Contractility (and SV) ↑ with:

1. Catecholamines (↑ activity of Ca^{2+} pump in sarcoplasmic reticulum)
2. ↑ intracellular calcium
3. ↓ extracellular sodium
4. Digitalis (↑ intracellular Na^+, resulting in ↑ Ca^{2+})

Contractility (and SV) ↓ with:

1. β_1 blockade
2. Heart failure
3. Acidosis
4. Hypoxia/hypercapnea
5. Non-dihydropyridine Ca^{2+} channel blockers

SV CAP.

SV ↑ in anxiety, exercise, and pregnancy.
A failing heart has ↓ SV.
Myocardial O_2 demand is ↑ by:

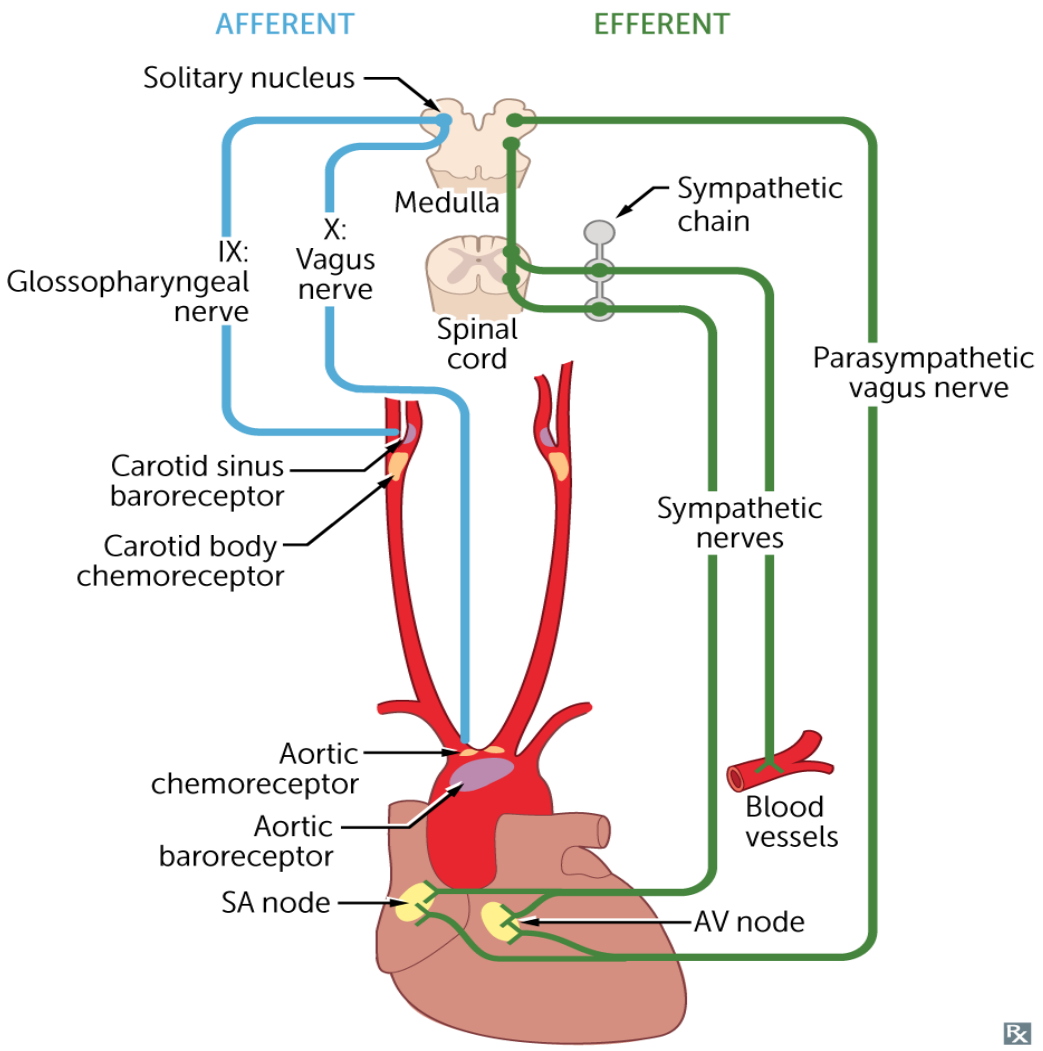
1. ↑ afterload (∝ arterial pressure)
2. ↑ contractility
3. ↑ heart rate
4. ↑ heart size (↑ wall tension)

Preload and afterload

Preload = ventricular EDV.
Afterload = mean arterial pressure (proportional to peripheral resistance).
Venodilators (e.g., nitroglycerin) ↓ preload.
Vasodilators (e.g., hydralazine) ↓ afterload.

Preload ↑ with exercise (slightly), ↑ blood volume (overtransfusion), and excitement (sympathetics).
Preload pumps up the heart.

Baroreceptors and chemoreceptors



Receptors:

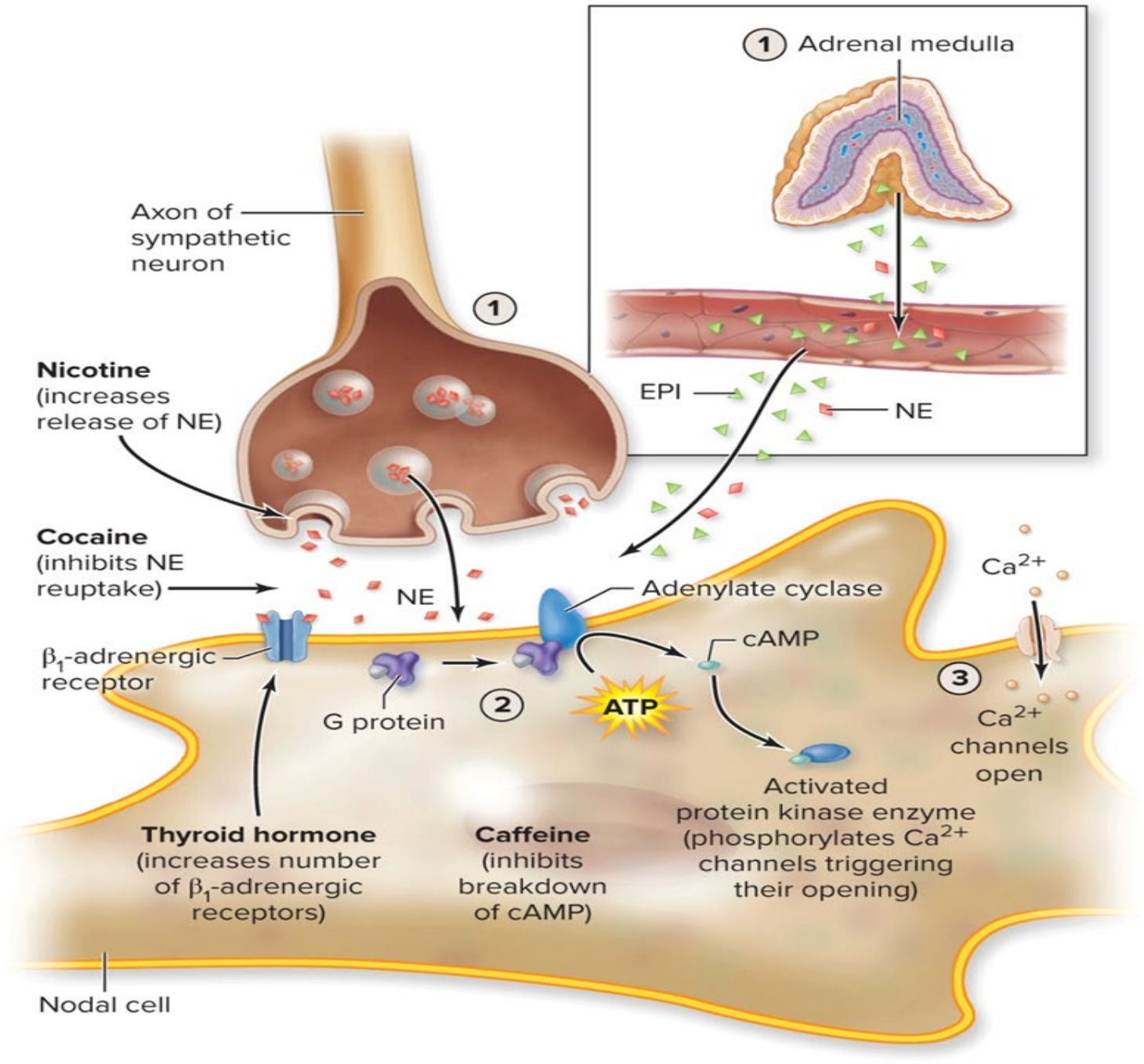
- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

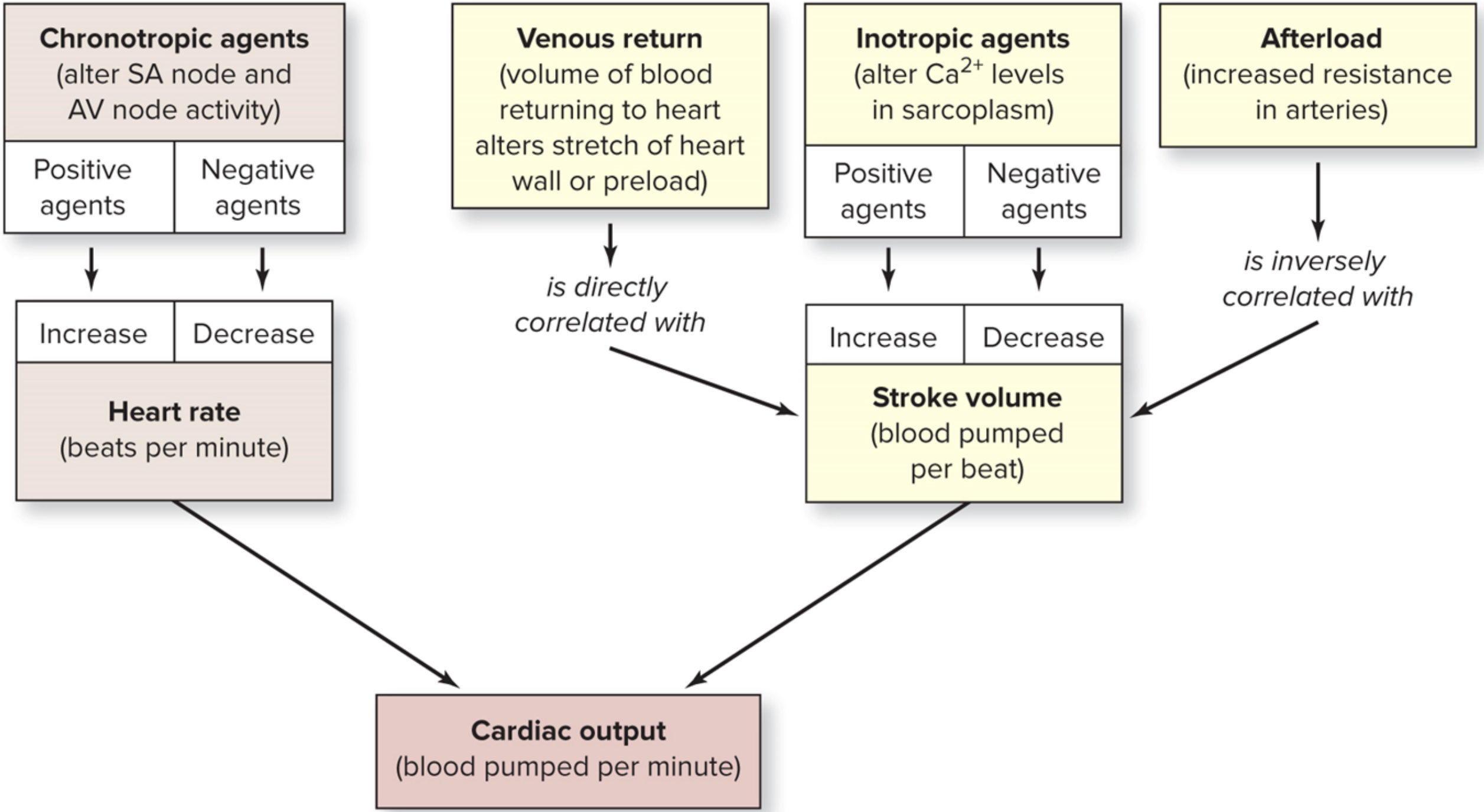
Baroreceptors:

- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
  - Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
  - Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO_2 and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor–induced bradycardia.

Chemoreceptors:

- Peripheral—carotid and aortic bodies are stimulated by ↓ Po_2 (< 60 mm Hg), ↑ Pco_2, and ↓ pH of blood.
- Central—are stimulated by changes in pH and Pco_2 of brain interstitial fluid, which in turn are influenced by arterial CO_2. Do not directly respond to Po_2.




Chronotropic agents
(alter SA node and AV node activity)
Positive agents
Negative agents
Increase
Decrease
Heart rate
(beats per minute)
Venous return
(volume of blood returning to heart alters stretch of heart wall or preload)
is directly correlated with
Inotropic agents
(alter Ca^{2+} levels in sarcoplasm)
Positive agents
Negative agents
Increase
Decrease
Stroke volume
(blood pumped per beat)
Afterload
(increased resistance in arteries)
is inversely correlated with
Cardiac output
(blood pumped per minute)

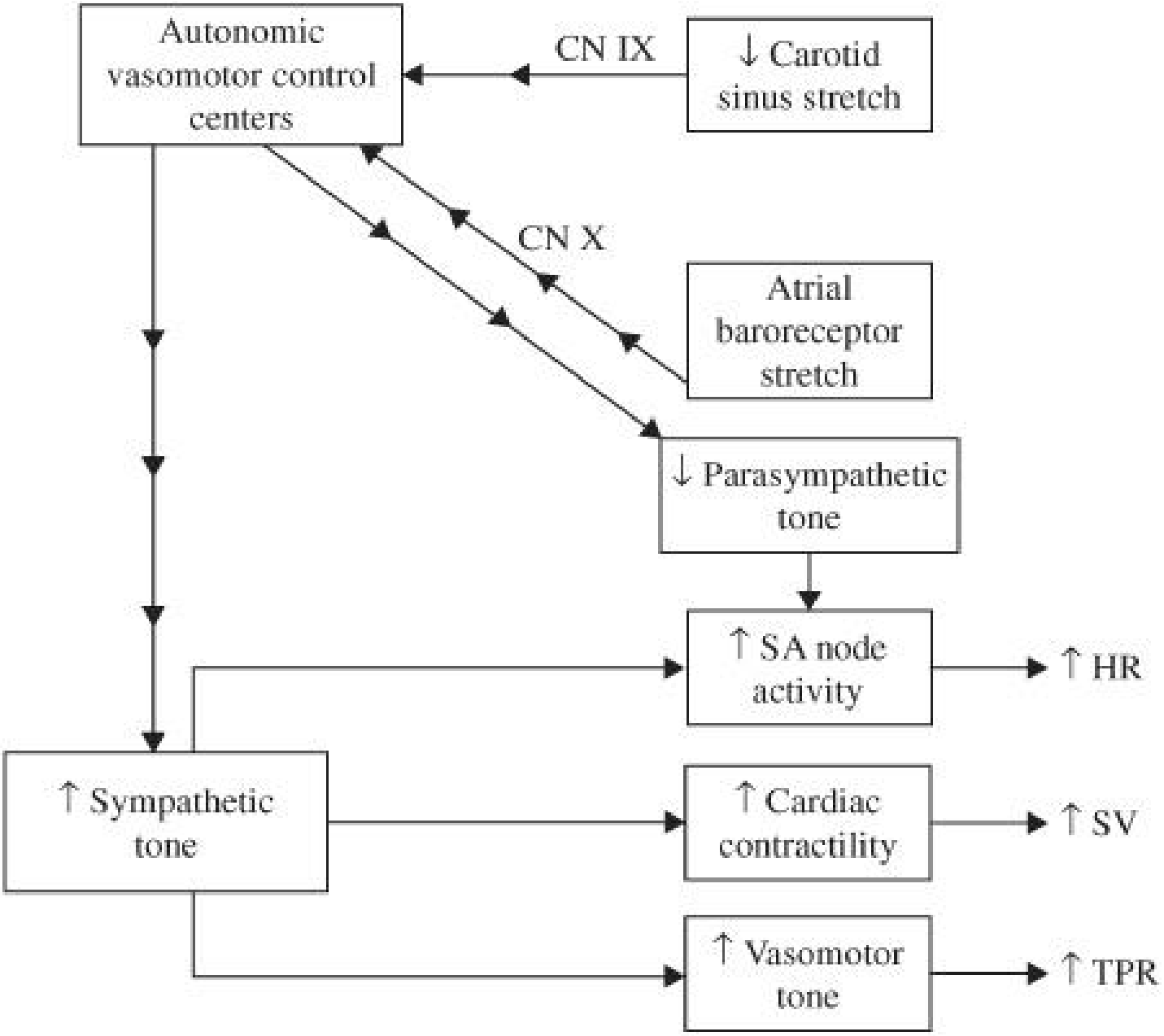
What is the primary difference between the two receptors?

Aortic arch baroreceptors primarily respond to *increases* in arterial pressures,

carotid receptors are more sensitive to *decreases* in arterial pressures

What are the steps in the baroreceptor reflex?

- The stretch receptors detect changes in vascular wall stretch. As pressure rises (or falls) the AP frequency in the afferent limb increases (or decreases).
- The autonomic response is coordinated by the vasomotor center and changes vascular tone to maintain normal blood pressure.



CN: Cranial Nerve, HR: Heart Rate, SV: Stroke Volume, TPR: Total Peripheral Resistance

What mediates the response of the vasomotor center?

- Changes in parasympathetic and sympathetic tone

What autonomic responses does the vasomotor center utilize to maintain blood pressure?

- Increased HR
- Increased contractility (with increased SV)
- Vasoconstriction of arterioles and veins

What happens during carotid massage?

- Massage stretches the walls of the carotid artery, which is interpreted as an elevated BP

Where are the peripheral chemoreceptors located?

- Carotid and aortic bodies

Carotid and aortic bodies

What do they respond to?

- Decreased PO_2
- Decreased pH of blood
- Increased PCO_2

Where are the central chemoreceptors located?

- Vasomotor center

Do the central chemoreceptors respond directly to PO_2?

- No

What do central chemoreceptors respond to?

- Decreases in pH and increased PCO_2 of brain interstitial fluid (CSF)

Regulation of Heart Rate

Positive chronotropic factors increase heart rate

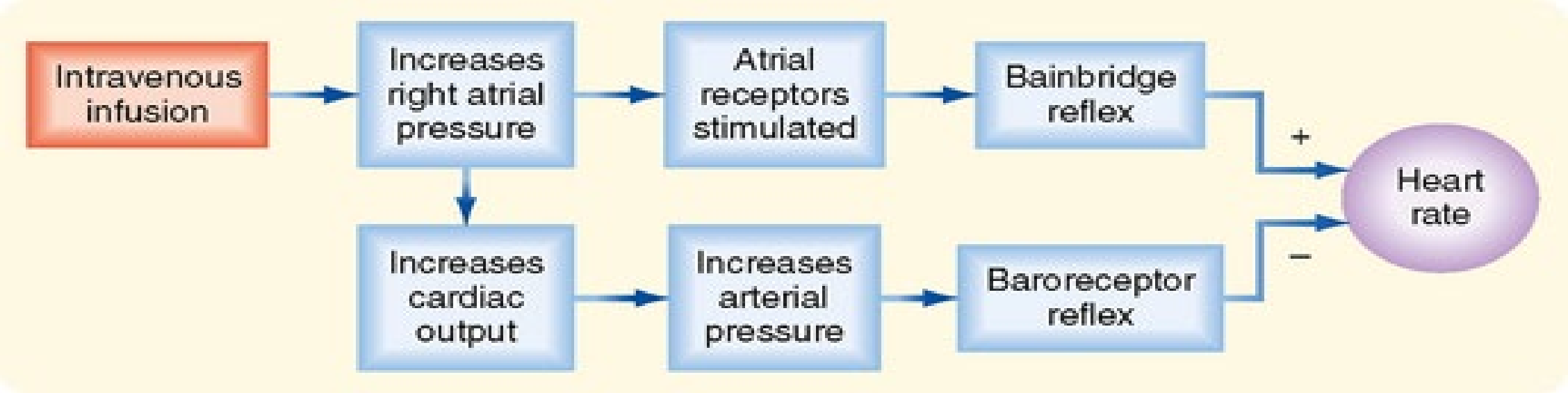
Negative chronotropic factors decrease heart rate

- **Sympathetic nervous system** (SNS) stimulation is activated by stress, anxiety, excitement, or exercise
- **Parasympathetic nervous system** (PNS) stimulation is mediated by acetylcholine and opposes the SNS
- **PNS** dominates the autonomic stimulation, slowing heart rate and causing vagal tone

Atrial (Bainbridge) Reflex

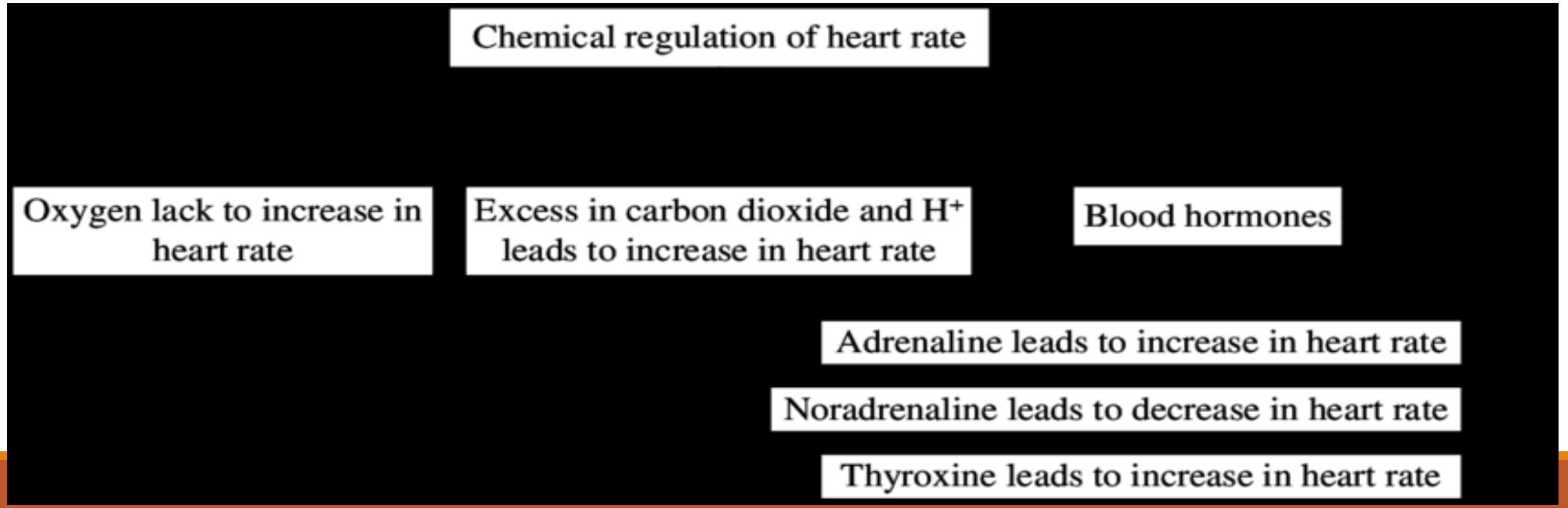
Atrial (Bainbridge) reflex – a sympathetic reflex initiated by increased blood in the atria

- Causes stimulation of the SA node
- Stimulates baroreceptors in the atria, causing increased SNS stimulation



Chemical Regulation of the Heart

- The hormones **epinephrine and thyroxine** increase heart rate
- Intra- and extracellular ion concentrations must be maintained for normal heart function



Factors Involved in Regulation of Cardiac Output

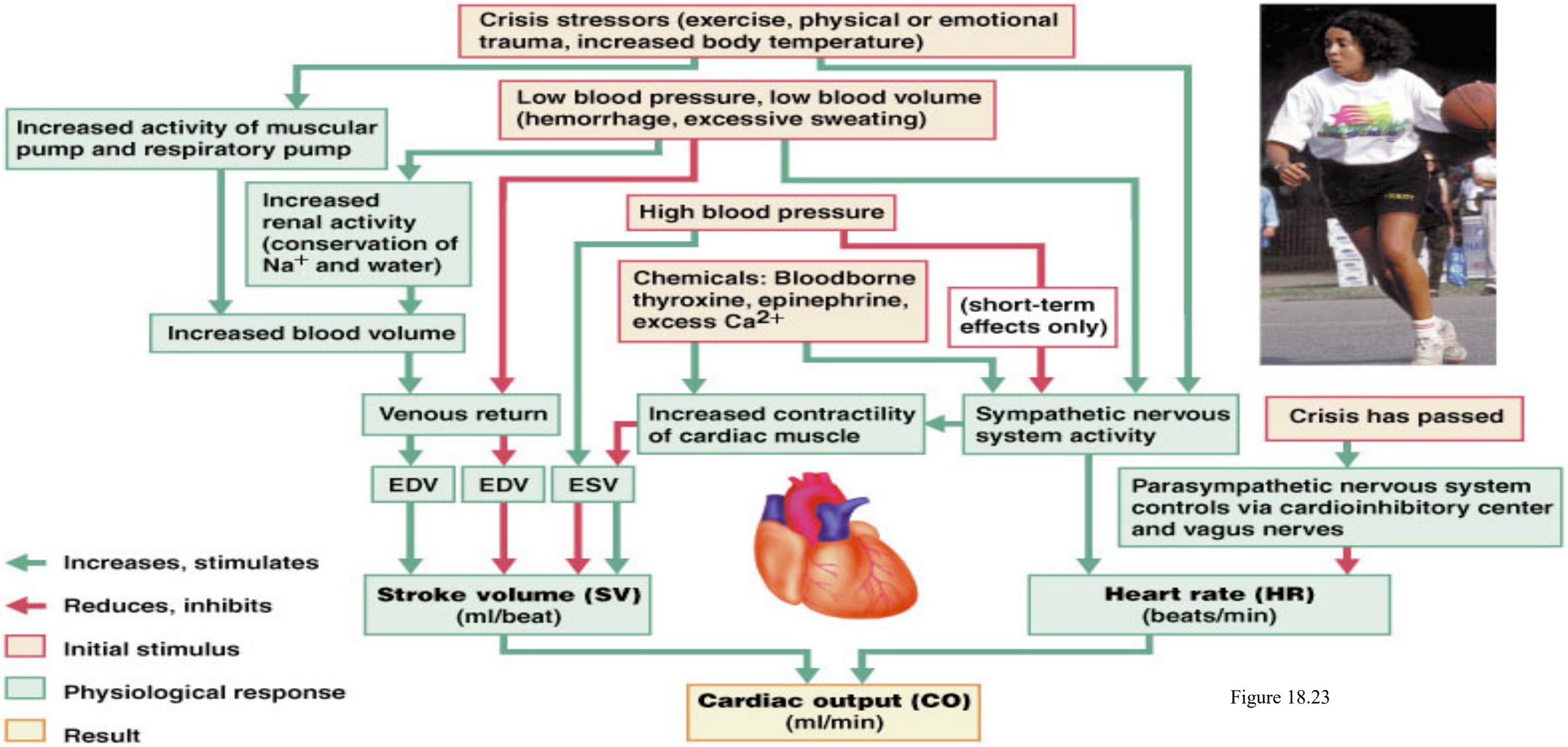


Figure 18.23

Circulation through organs

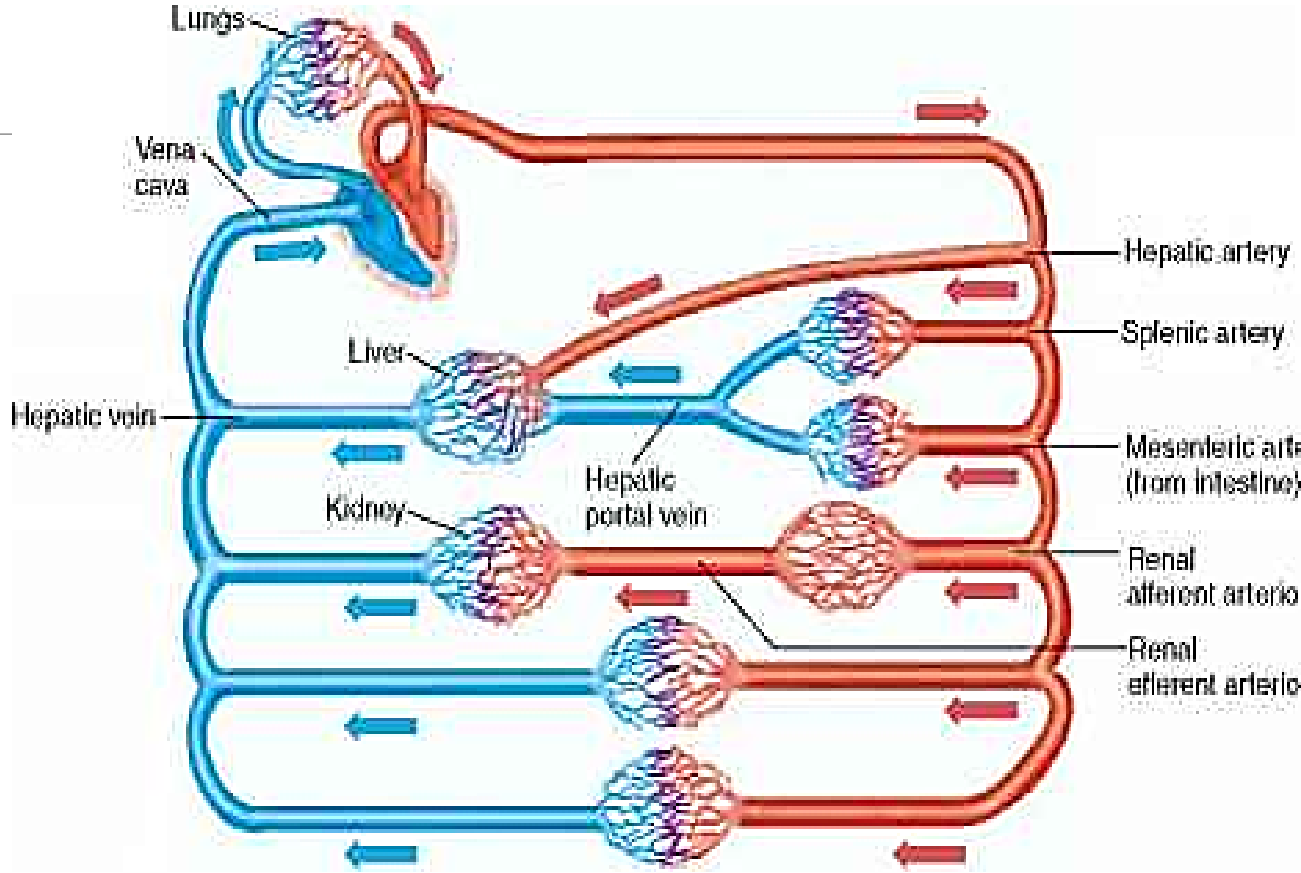
Liver	Largest share of systemic cardiac output.
Kidney	Highest blood flow per gram of tissue.
Heart	Large arteriovenous O_2 difference. ↑ O_2 demand is met by ↑ coronary blood flow, not by ↑ extraction of O_2.

Autoregulation

Organ	Factors determining autoregulation
Heart	Local metabolites—O_2, adenosine, NO
Brain	Local metabolites—CO_2 (pH)
Kidneys	Myogenic and tubuloglomerular feedback
Lungs	Hypoxia causes vasoconstriction
Skeletal muscle	Local metabolites—lactate, adenosine, K^+
Skin	Sympathetic stimulation most important mechanism—temperature control

Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction. In other organs, hypoxia causes vasodilation.

Regulation of blood circulation



Mechanisms of regulation:

Local

- Humoral (chemical) – O_2, CO_2, H^+
- Nervous
- Enzymatic and hormonal

General

- **Fast** = short-term (regulate blood pressure)
- **Slow** = long-term (regulate blood volume) – several days

Local chemical regulatory mechanisms

The most obvious in the heart and the brain

Goal: autonomic regulation of resistance by organ based on its metabolic needs

Principal: accumulation of products of metabolism (CO_2, H^+, lactacid) or consumption of substances necessary for proper function (O_2) directly affects smooth muscles of vessels and induce **vasodilatation**

Local nervous regulatory mechanisms

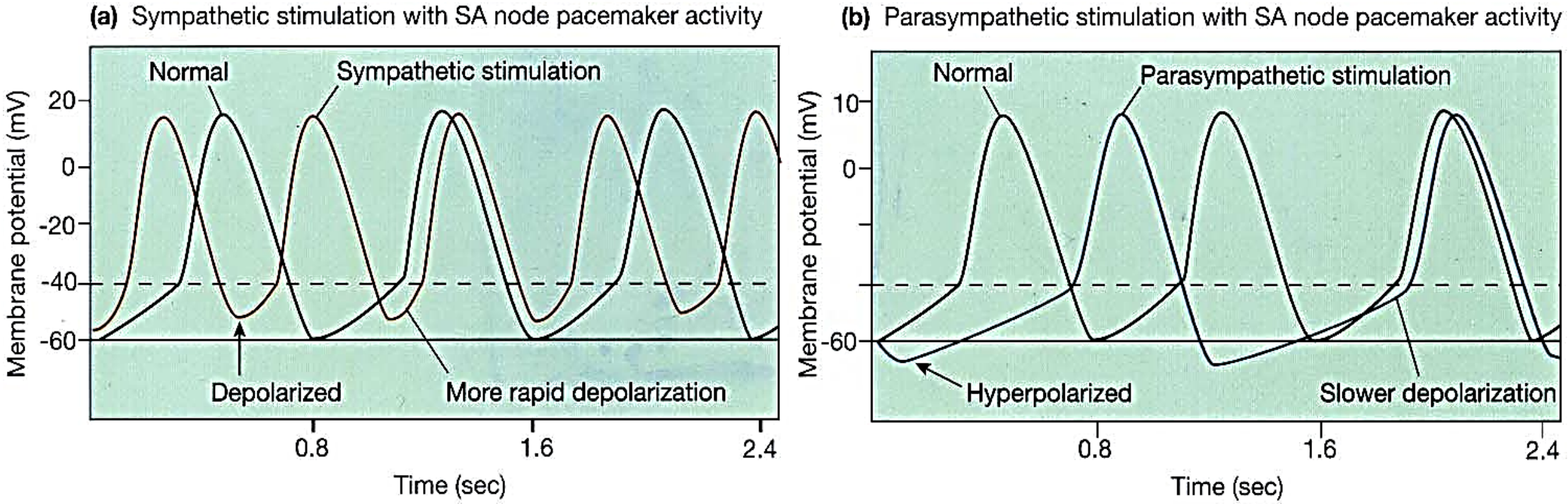
The most obvious in the **skin and mucous**

Goal: central regulation of blood distribution

Principal: Autonomic nervous system

- **Sympaticus**
  - **Vasoconstriction** – activation of **α** receptors in vessels- noradrenalin (glands, GIT, skin, mucous, kidneys, other inner organs)
  - **Vasodilatation** – activation of **β** receptors in vessels – adrenalin (heart, brain, skeletal muscles)
- **Parasympaticus** - Acetylcholin
  - **Vasoconstriction** – heart
  - **Vasodilatation** – salivatory glands, GIT, external genitals

Neural Control of Heart Rate



Noradrenaline (NA) from sympathetic nerves and circulating adrenaline, increase the heart rate and enhances conduction of the AP.

Acetylcholine (ACh) released from parasympathetic nerves reduces the heart rate and conduction across the AV node.

Local enzymatic and hormonal regulatory mechanisms

Kinin ↑ = vasodilatation

- Cells of GIT glands contain **kallikrein** – changes kininogen to kinin → kallidin → **bradykinin** (vasodilatation)
- **Kinins** are any of various structurally related polypeptides, such as bradykinin and kallikrein, that act locally to induce vasodilation and contraction of smooth muscle.
- A role in inflammation, blood pressure control, coagulation and pain.

Hormones of adrenal medula: adrenalin (vasodilatation), noradrenalin (vasoconstriction)

General fast (short-term) regulatory mechanisms (1)

Nervous autonomic reflexes

- **Baroreflex**
  - **glomus caroticum, glomus aorticum**
  - **Afferentation**: IX and X spinal nerve
  - **Centre:** medulla oblongata, nucleus tractus solitarii
  - **Efferentation**: X spinal nerve, sympatetic fibres
  - **Effector:** heart (atriums), vessels
  - **Effect:** After acute increase of blood pressure – activation of receptors **– decrease of blood pressure (vasodilatation, decrease of effect of sympaticus)**

General fast (short-term) regulatory mechanisms (2)

Receptors in the heart

- **Reflex of atrial receptors** – **mechano- and volumoreceptors** – activated by increased blood flow through the heart
  - A receptors – **sensitive to ↑ of wall tension after systole of atriums**
  - B receptors – **sensitive to ↑ of wall tension after systole of ventricles**

- **Ventricular receptors** – mechano- and chemical receptors - activated in pathological cases
  - Hypoxia of myocardium → decrease of heart rate **(Bezold-Jarisch reflex)** → protection of myocardium of larger damage

Humoral mechanisms

- **Adrenalin** – β receptors → vasodilatation → ↓ peripheral resistance → blood from skin and GIT to skeletal muscles, heart and brain → **↑ minute heart volume**
- **Noradrenalin** – α receptors → vasoconstriction → **↑ blood pressure**
- **Renin-angiotensin** – activated by ↓ pressure in vas afferens

General slow (long-term) regulatory mechanisms

Regulatory mechanisms of water and electrolytes exchanges

Regulation of total blood volume by kidneys

- When ↑ blood pressure → ↑ of filtration pressure in glomeruli → ↑ production of urine → ↓ volume of circulating blood → ↓ blood pressure

Increase of ADH (vasopressin)

- ↑ ADH → ↑ of the permeability of collecting ductus for the water → water is reabsorbed → ↑ volume of circulating blood → ↑ blood pressure

Increase of Aldosterone

- ↑ aldosterone → ↑ reabsorbtion Na^+ and water → ↓ volume of urine → ↑ volume of circulating blood → ↑ blood pressure

Intracardial regulatory mechanisms

Ionotropic effect of heart rhythm

- **↑ heart frequency** → ↑ amount of Ca^{2+} that goes into heart cells → ↑ Ca^{2+} available for tubules of sarkoplasmatic reticulum → ↑ Ca^{2+} that is freed by each contraction → **↑ strength of contraction**

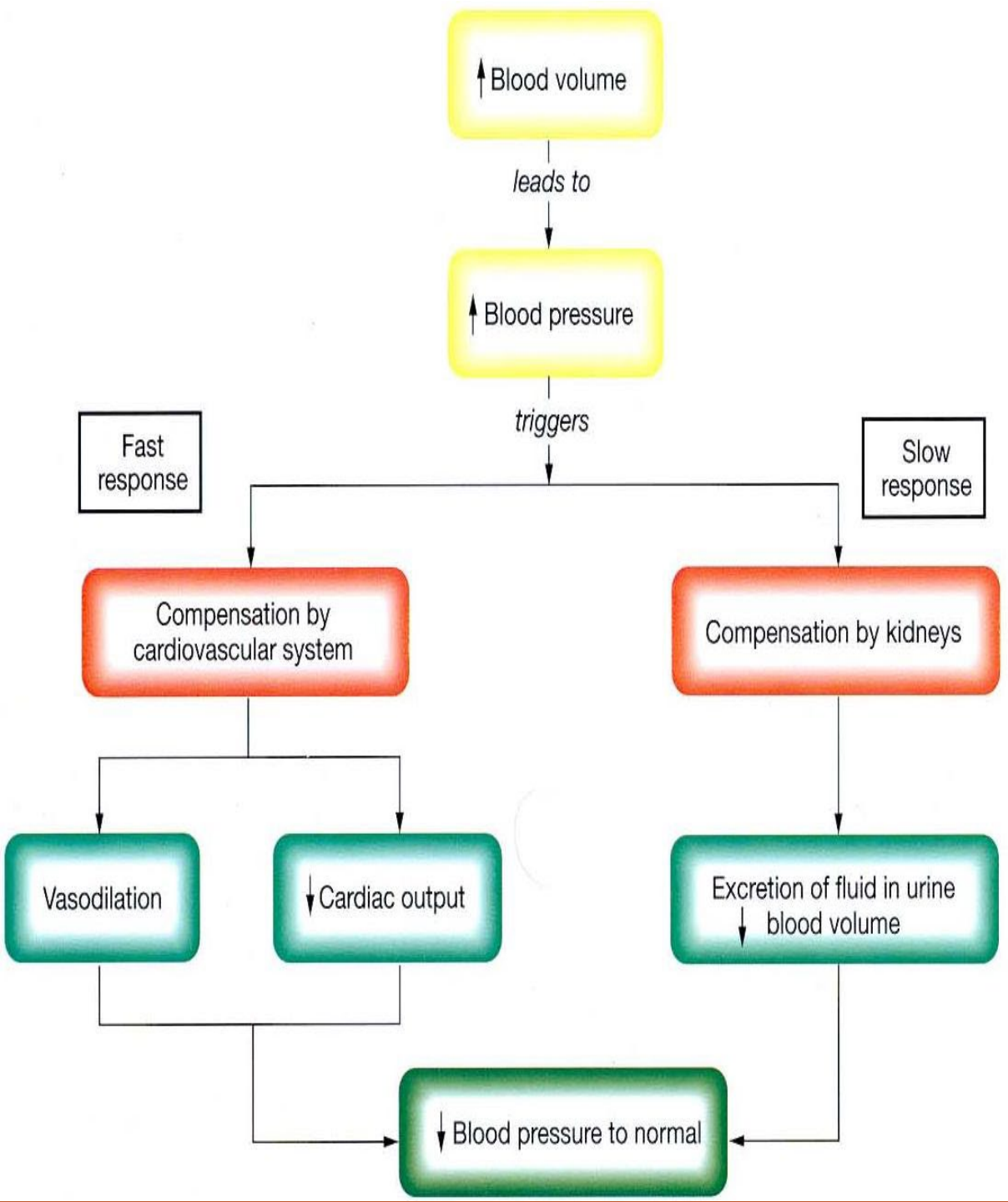
Extracardial regulatory mechanisms

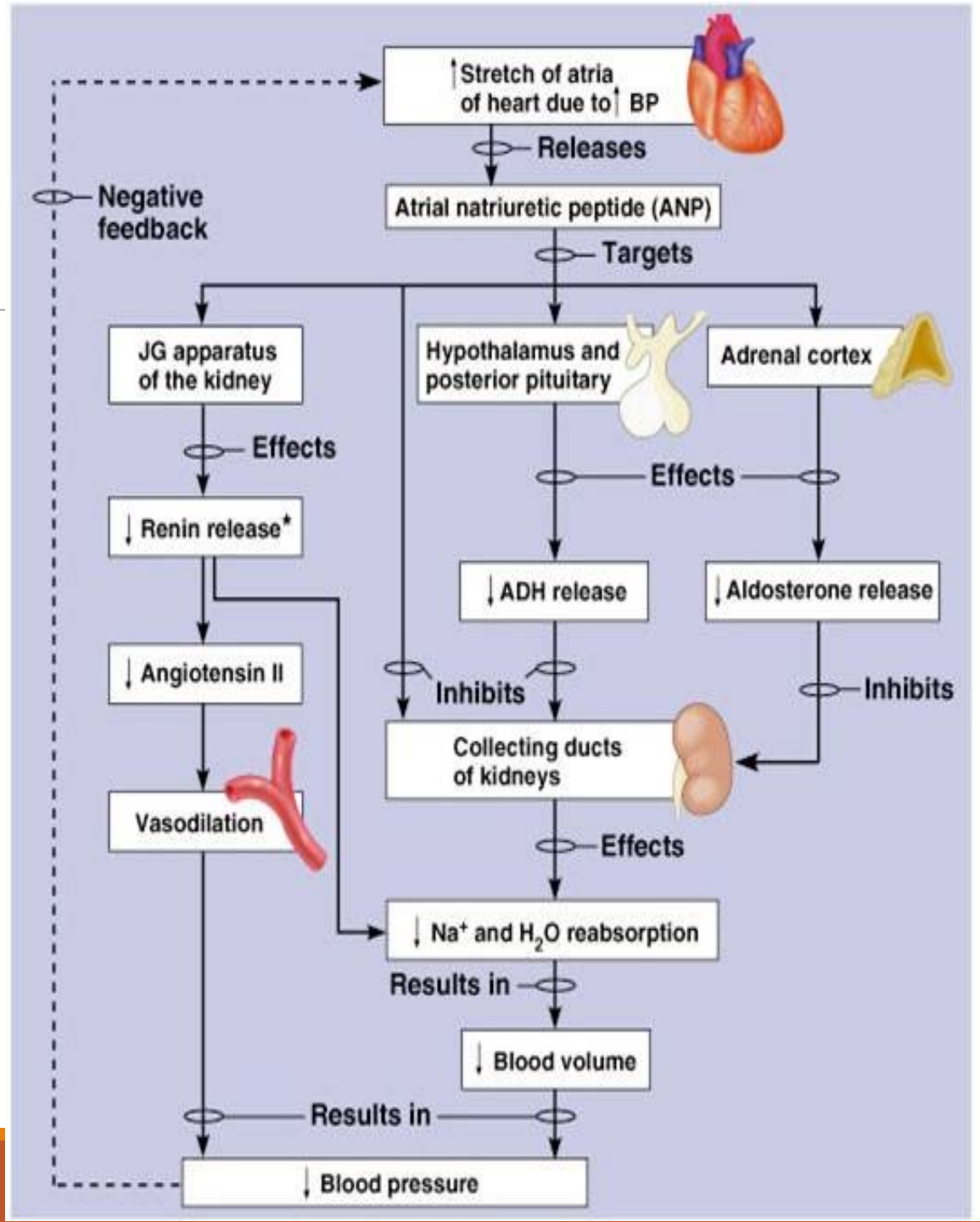
Cardiomotoric centers

- **Inhibition** – ncl. Ambiguus (beginning of n. vagus in medulla oblongata)
- **Excitation** - Th1-3 beginning of sympathetic fibres

Vasomotoric centers

- In **brain stem** (medulla oblongata, Pons Varoli)
- In the **hypothalamus** (controls activity of **vasomotoric centers in brain stem**)
- **Brain cortex** – control both the **hypothalamus and the brain stem**


↑Blood volume
leads to
↑Blood pressure
triggers
Fast response
Slow response
Compensation by cardiovascular system
Compensation by kidneys
Vasodilation
↓Cardiac output
Excretion of fluid in urine
↓blood volume
↓Blood pressure to normal


↑Stretch of atria of heart due to↑ BP
Releases
Atrial natriuretic peptide (ANP)
Negative feedback
Targets
JG apparatus of the kidney
Hypothalamus and posterior pituitary
Adrenal cortex
Effects
Effects
↓Renin release*
↓ADH release
↓Aldosterone release
↓Angiotensin II
Inhibits
Inhibits
Collecting ducts of kidneys
Vasodilation
Effects
↓Na+ and H2O reabsorption
Results in
↓Blood volume
Results in
↓Blood pressure

Resistance, pressure, flow

$\Delta P = Q \times R$

Similar to Ohm's law: $\Delta V = IR$.

$$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

Viscosity depends mostly on hematocrit.

Viscosity ↑ in:

1. Polycythemia
2. Hyperproteinemic states (e.g., multiple myeloma)
3. Hereditary spherocytosis

Resistance is directly proportional to viscosity and inversely proportional to the radius to the 4th power.

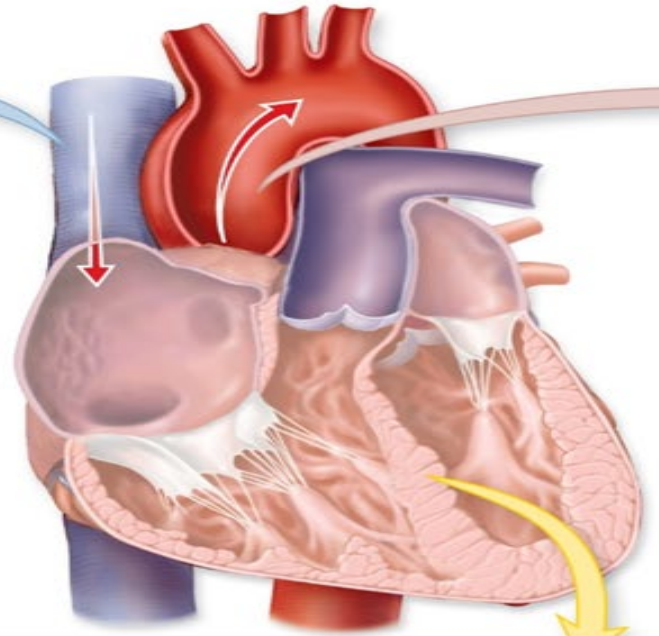
Arterioles account for most of total peripheral resistance → regulate capillary flow.

Ejection fraction (EF)

$$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

EF is an index of ventricular contractility.

EF is normally ≥ 55%.



(a) Venous return

Volume of blood returned to the heart per unit time

- Increased venous return (occurs with greater venous pressure or slower heart rate)
- Increases stretch of the heart wall (preload), which results in greater overlap of thick and thin filaments within the sarcomeres of the myocardium
- Additional crossbridges form, and ventricles contract with greater force
- Stroke volume increases

The opposite is seen with smaller venous return (e.g., occurs with hemorrhage or extremely rapid heart rate)

(b) Inotropic agents

Substances that act on the myocardium to alter contractility

- Positive inotropic agents (e.g., stimulation by sympathetic nervous system)
- Increased Ca^{2+} levels in the sarcoplasm result in greater binding of Ca^{2+} to troponin of thin filaments within sarcomeres of the myocardium
- Additional crossbridges form, and ventricles contract with greater force
- Stroke volume increases

The opposite is seen with negative inotropic agents (e.g., calcium channel blockers)

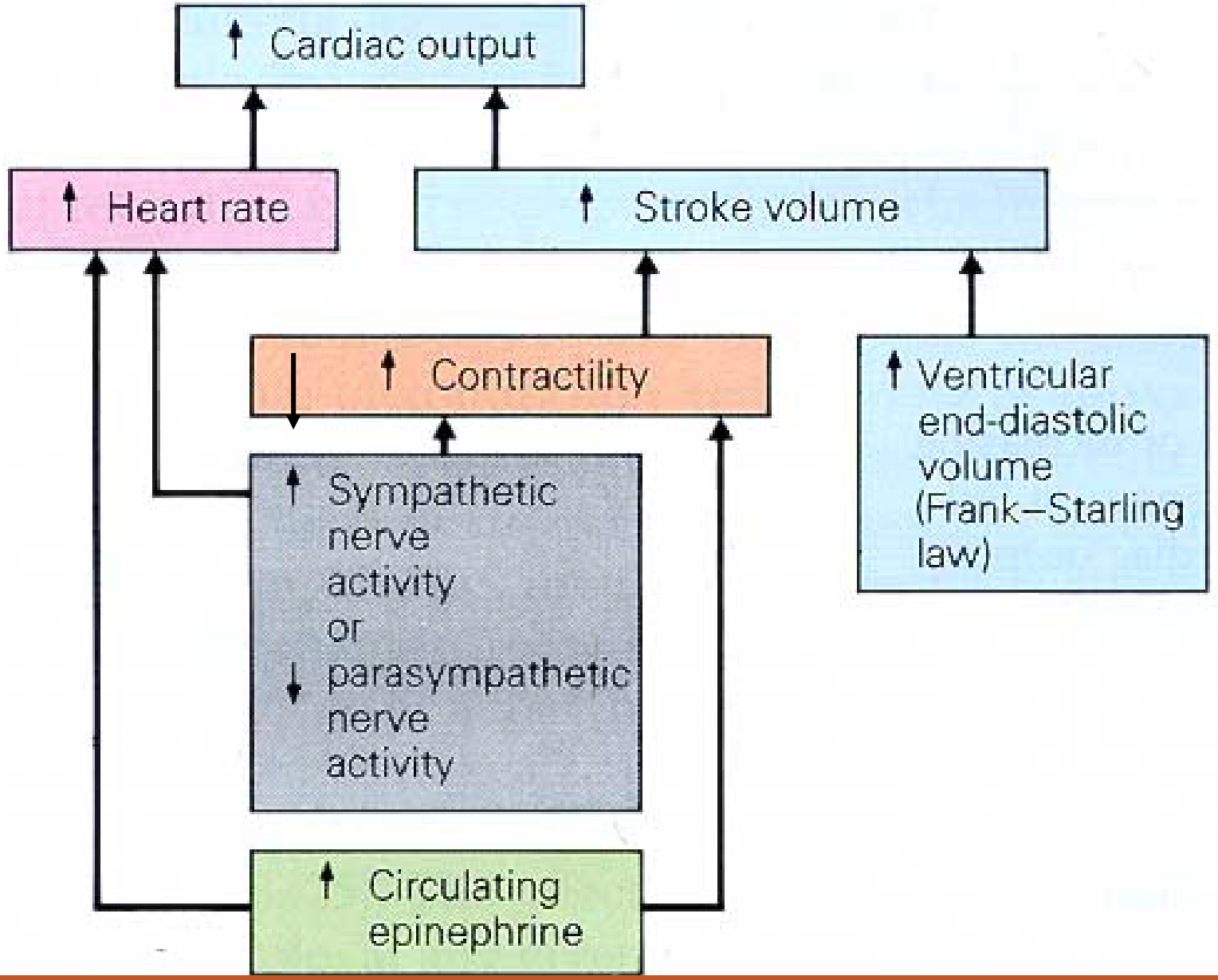
(c) Afterload

Resistance in arteries to ejection of blood

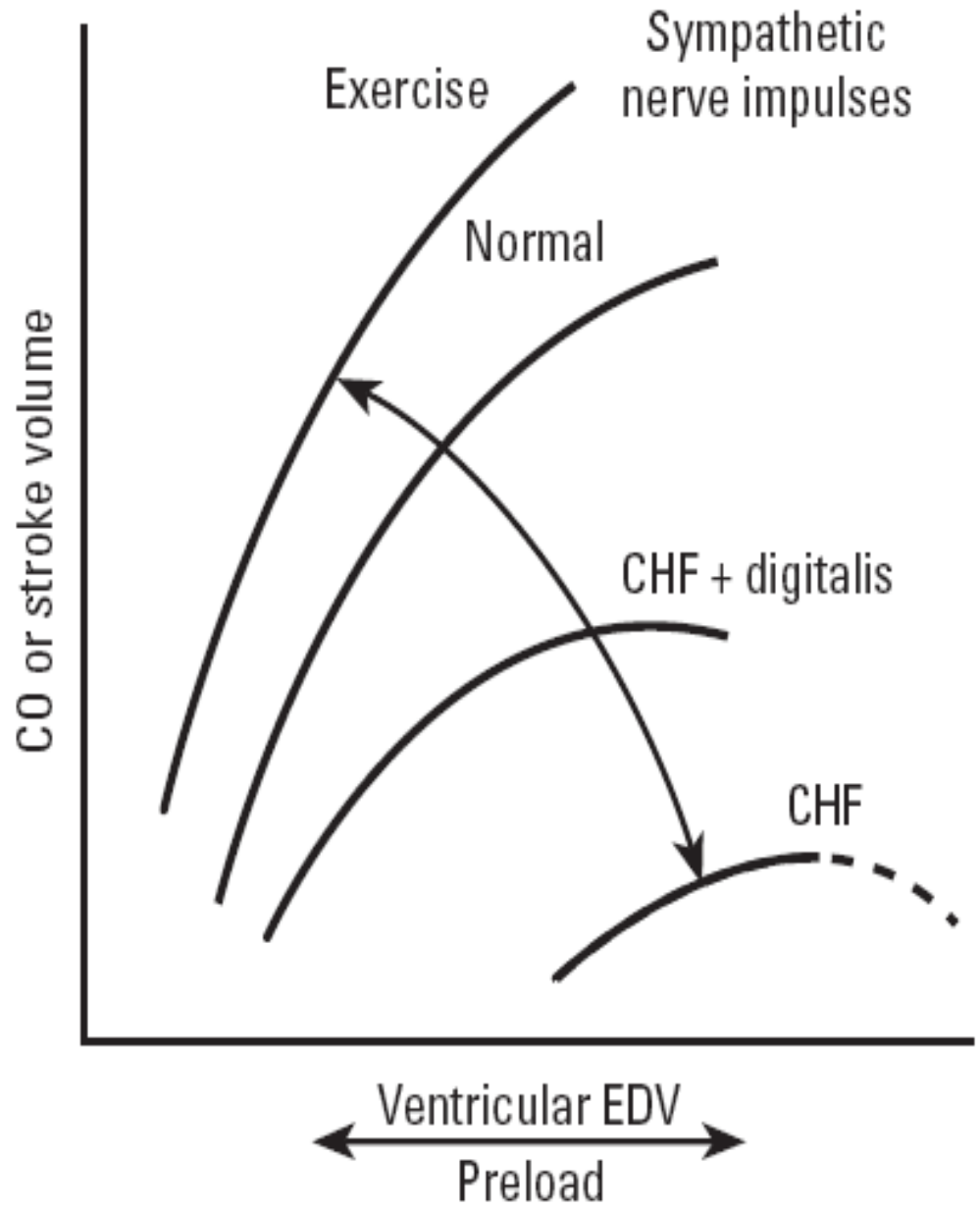
- Atherosclerosis, which is deposition of plaque on the inner lining of arteries, is typically only a factor as we age
- Arteries become more narrow in diameter
- Increases the resistance to pump blood into the arteries
- Stroke volume decreases

Control of the Heart

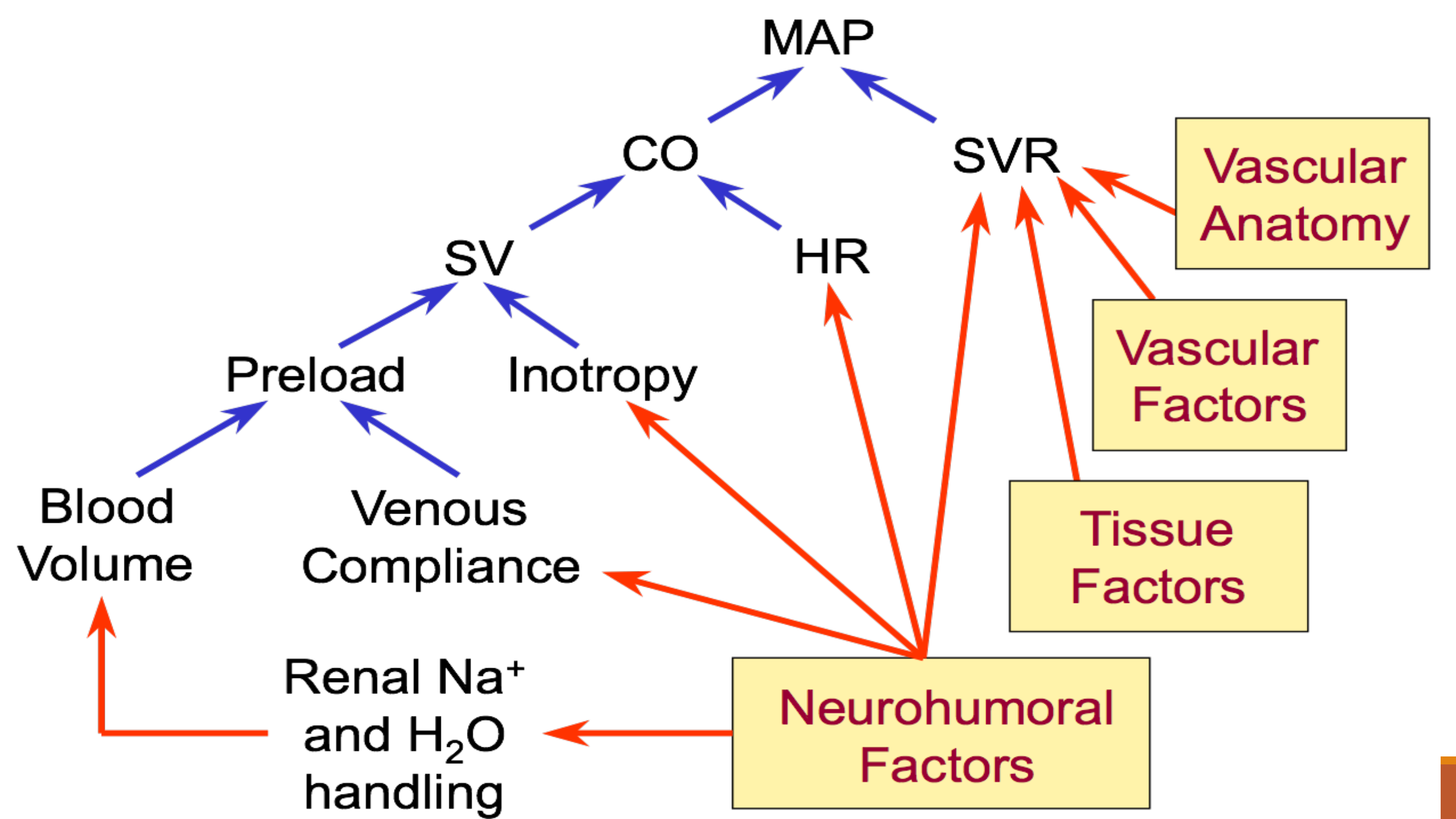
Summary of mechanisms that affect cardiac output.



Starling curve Force of contraction is proportional to initial length of cardiac muscle fiber (preload).



CONTRACTILE STATE OF MYOCARDIUM	
⊕	⊖
Circulating catecholamines	Pharmacologic depressants
Digitalis	Loss of myocardium (MI)
Sympathetic stimulation	


MAP
CO
SVR
SV
HR
Preload
Inotropy
Blood Volume
Venous Compliance
Renal Na+ and H2O handling
Neurohumoral Factors
Vascular Anatomy
Vascular Factors
Tissue Factors

Factors Controlling Blood Pressure

♥↑ Peripheral resistance	↑ mean arterial pressure
♥↑Cardiac output	↑ mean arterial pressure
♥↑Stroke volume	↑ pulse pressure
♥↓ Arterial compliance	↑pulse pressure
♥↑Heart Rate	↓pulse pressure
♥↑Blood Volume	↑ arterial & venous

What two physiologic systems are primarily responsible for BP management?

1. Baroreceptor reflex
2. Renin-angiotensin system

Through what reflex is the body able to quickly regulate the minute-to-minute arterial blood pressure?
Baroreceptor reflex

How is the baroreceptor reflex mediated?
It is a neurally mediated negative feedback system

What are baroreceptors?
Stretch receptors
Where are they located?
The primary receptors can be found at the bifurcation of the common carotids; another set is located in the aortic arch.

What do the baroreceptors respond to?
- Carotid sinus baroreceptors: stretch of the sinus walls
- Aortic arch receptors: increases in aortic wall tension

What nerves do the baroreceptors utilize to regulate blood pressure?
- Carotid sinus baroreceptors: glossopharyngeal nerve (CN IX)
- Aortic arch baroreceptors: vagus nerve

Vascular Baroreceptor Reflex

- Reduced arterial blood pressure decreased baroreceptor activity.
- Increased sympathetic tone to blood vessels.
- Elevated total peripheral resistance and blood pressure.
- (Coronary and cerebral circulation are largely unaffected.)
- Elevated venous tone.
- Reduced venous capacitance, reduced venous volume.
- Increased circulating volume, increased venous return.
- Increased stroke volume, cardiac output and blood pressure.

Acute Autoregulation

Three mechanisms have been suggested to explain acute autoregulation.

1) Myogenic mechanisms

2) Tissue pressure

3) local metabolites

Myogenic Mechanism

- **Increased pressure increases arteriolar wall tension.**
- **Vascular smooth muscle contracts when stretched and relaxed when passively shortened.**
- **Action is purely myogenic, no mediators required.**
- **Involves stretch sensitive ion channels on the cell membrane.**

Summary of Metabolic Mediators

- **O_2 Vasoconstrictor (not pulmonary)(import. brain)**
- **Glucose: vasoconstrictor (at least coronary vessels)**
- **K^+ Vasodilator (skeletal muscle)**
- **CO_2 vasodilator (not pulmonary)(import. brain)**
- **Adenosine vasodilator (coronary)**
- **H^+ vasodilator (import. brain)**
- **PO_4^{3-} vasodilator**
- **Osmolarity vasodilator**

Inputs to blood pressure control includes

- Sympathetic activity
- Parasympathetic activity
- Chemical secretion
- Kidney

Kidney activity regulation

Kidney regulates the secretion of:

- **Renin**
- **Angiotensin II**
- **Aldosterone**

Renin and Angiotensin II controls Total Peripheral Resistance.

Aldosterone controls the urine output.

Pressure Diuresis

- **Increased arterial pressure increases filtration and urine production.**
- **Increased urine production reduces extracellular fluid (ECF) and blood volume.**

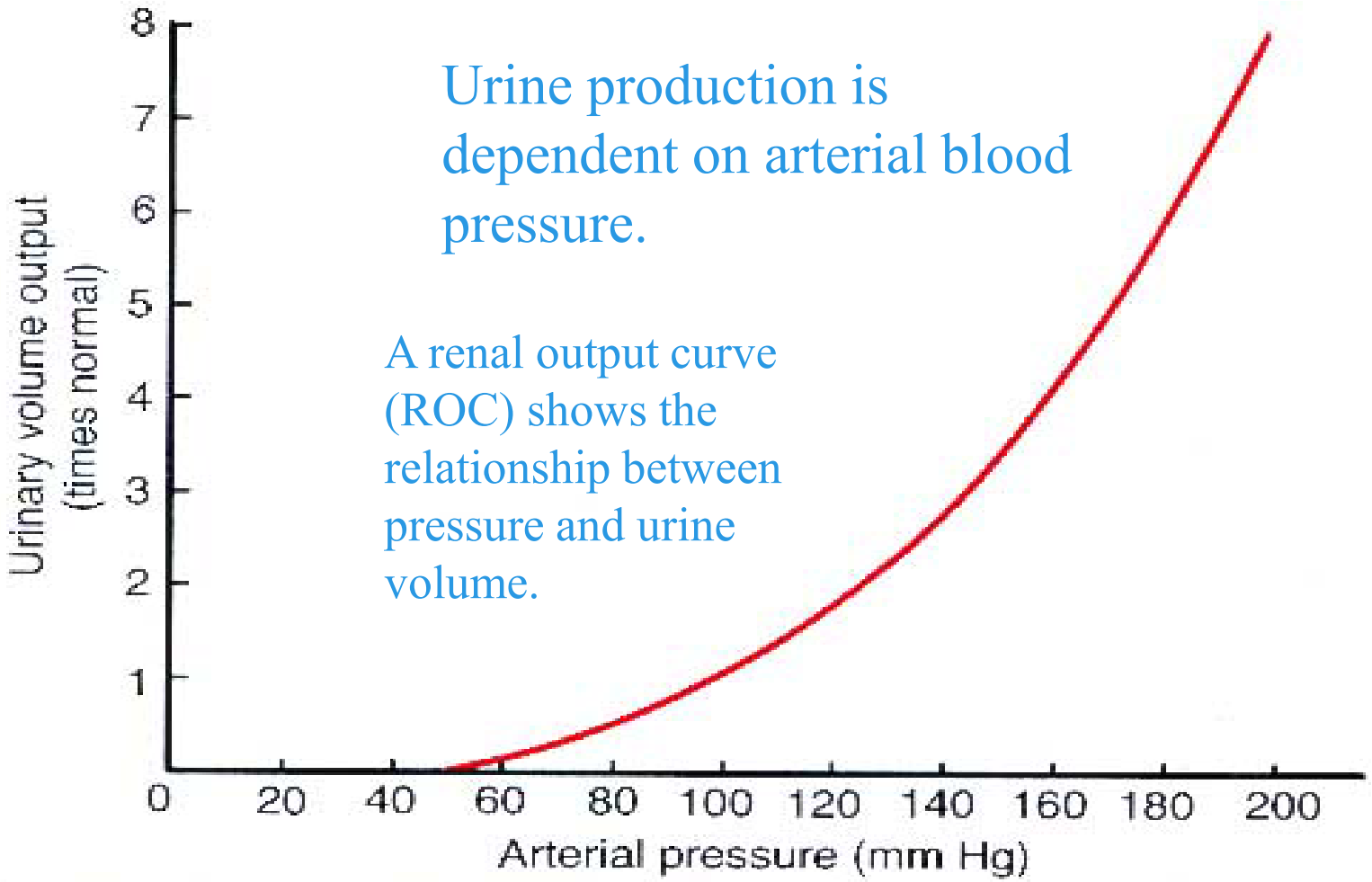


Figure 19–1. A typical renal output curve measured in a perfused isolated kidney, showing pressure diuresis when the arterial pressure rises above normal.

- ECF volume is continually lost as urine.
- ECF volume is maintained only if intake is sufficient to balance loss.
- Loss of ECF volume is dependent on blood pressure.
- Increased blood pressure increases ECF volume loss and blood pressure falls.
- Net loss of ECF stops when blood pressure is sufficient for ECF loss from urine to just balances fluid intake.
- Imbalance in osmolarity is controlled by the osmoreceptor system.
- Salt load is generaly more important than water as the osmoreceptors regulate water to the salt load.

How is resistance regulated physiologically?
Through the autonomic nervous system which modulates the tone of vascular smooth muscle to change vessel radius

Which component of the vascular system is the site of the highest resistance?
The arterioles; these have the greatest ability to change their radius, and, therefore, their resistance

What factors change the resistance of the vasculature system proportionally?
Viscosity and length of the vessel

What is the major determinant of viscosity in the vascular system?
The hematocrit is mostly responsible for the viscosity within the vascular system

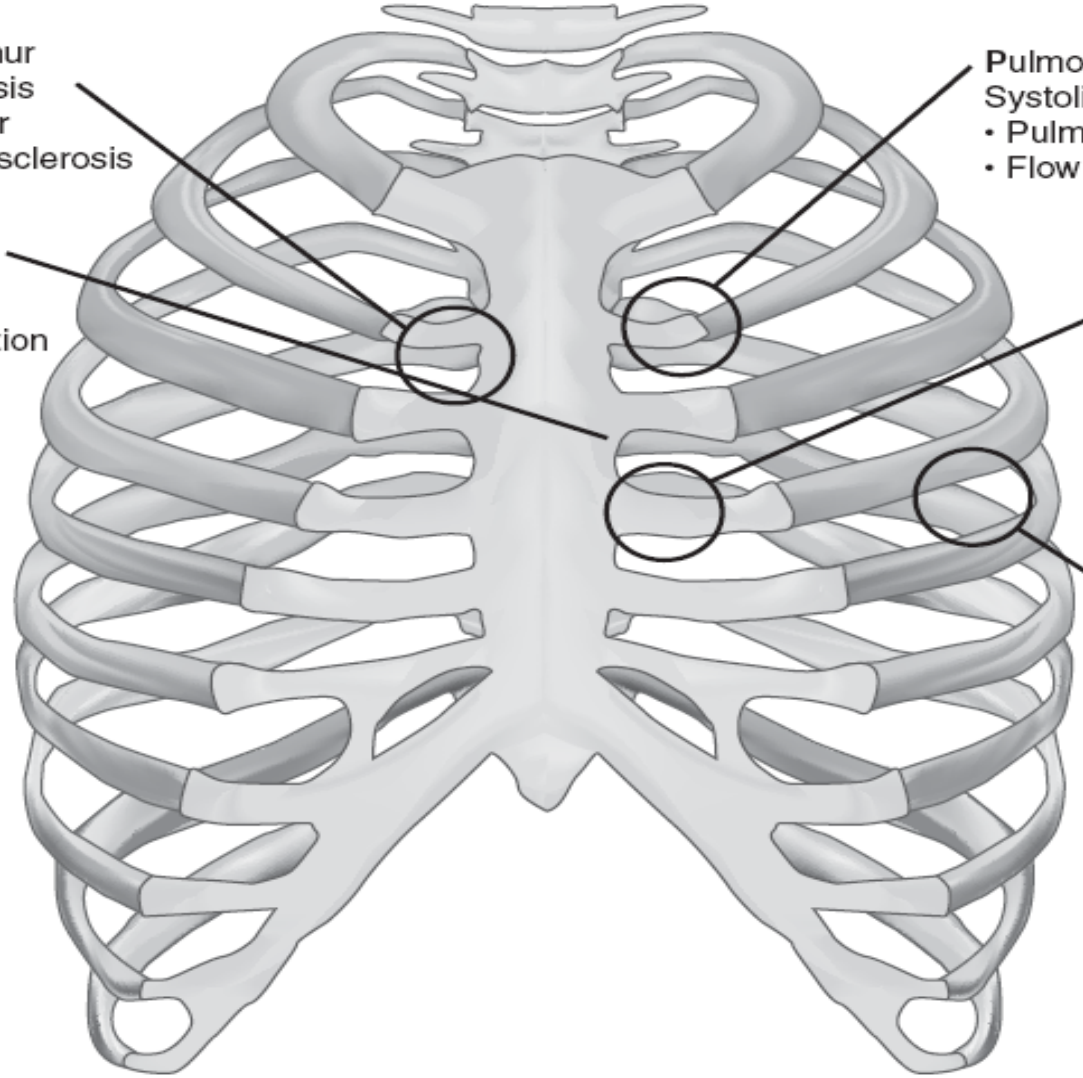
In what pathologic states does viscosity increase?
- Polycythemia
- Hyperproteinemia
- Hereditary spherocytosis

Auscultation of the heart

Where to listen:
APT M

Aortic area:
Systolic murmur
- Aortic stenosis
- Flow murmur
- Aortic valve sclerosis

Left sternal border:
Diastolic murmur
- Aortic regurgitation
- Pulmonic regurgitation



Pulmonic area:
Systolic ejection murmur
- Pulmonic stenosis
- Flow murmur (e.g., atrial septal defect)*

Tricuspid area:
Pansystolic murmur
- Tricuspid regurgitation
- Ventricular septal defect

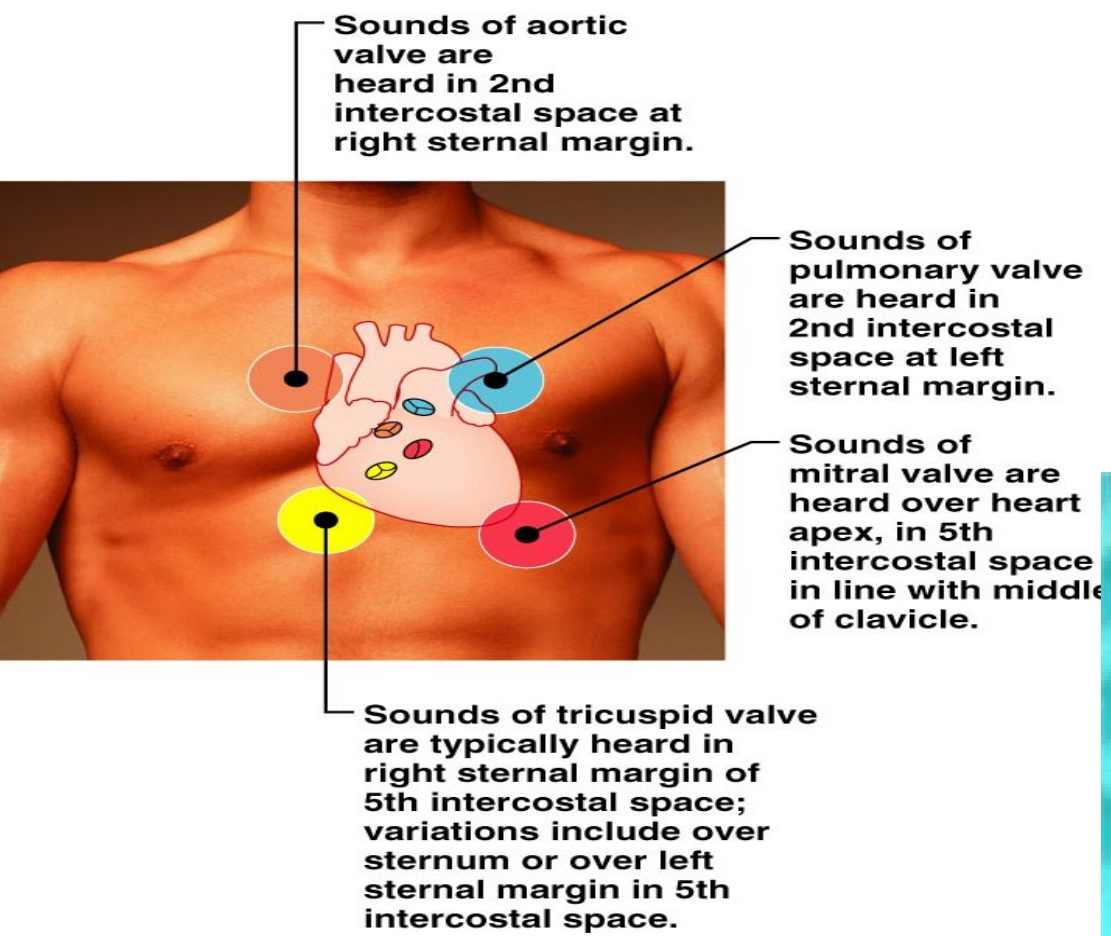
Diastolic murmur
- Tricuspid stenosis
- Atrial septal defect*

Mitral area:
Systolic murmur
- Mitral regurgitation

Diastolic murmur
- Mitral stenosis

*ASD commonly presents with a pulmonary flow murmur (↑ flow through pulmonary valve) and a diastolic rumble (↑ flow across tricuspid). The murmur later progresses to a louder diastolic murmur of pulmonic regurgitation from dilatation of the pulmonary artery.

Heart Sounds



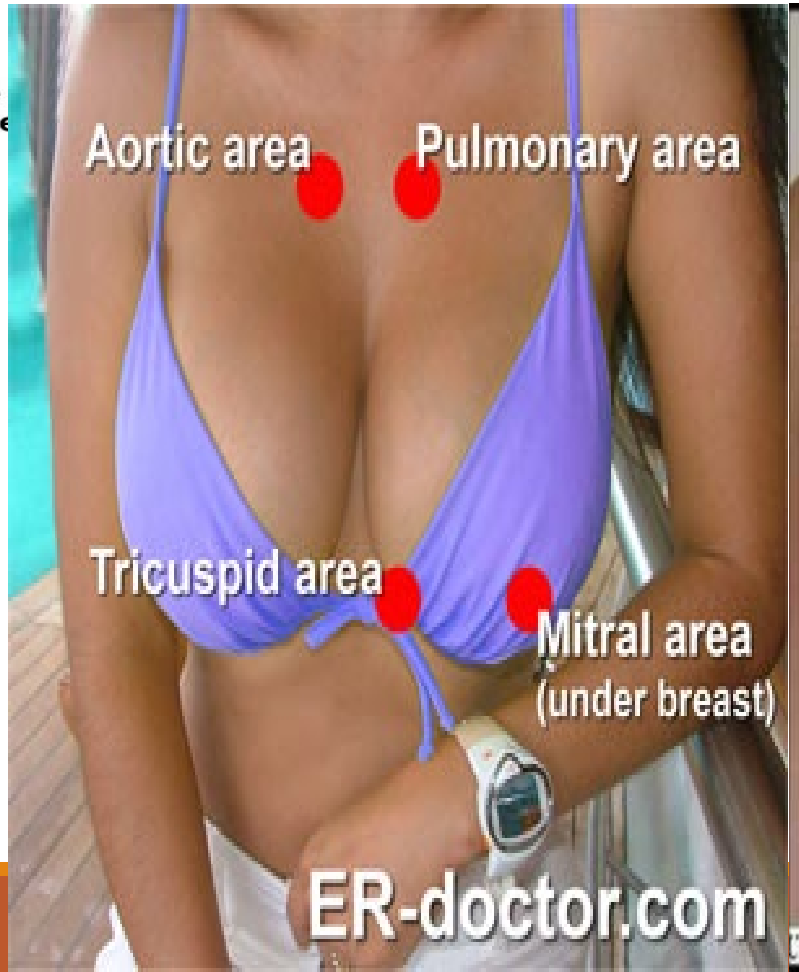
S4

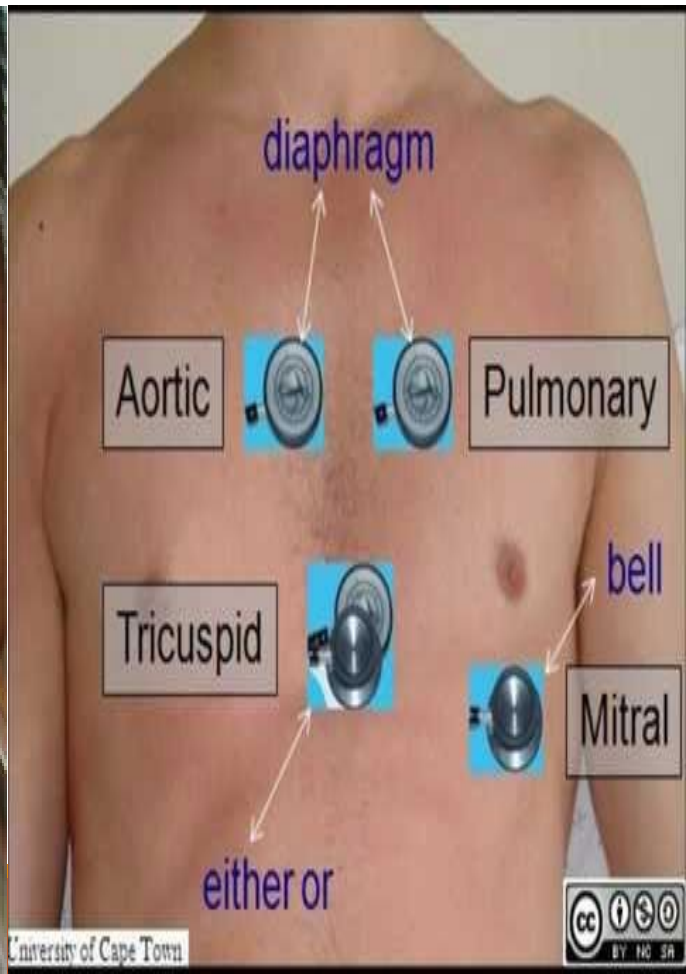
S1 = Mitral,Tricuspid then pulmonary artery valve,aortic valve

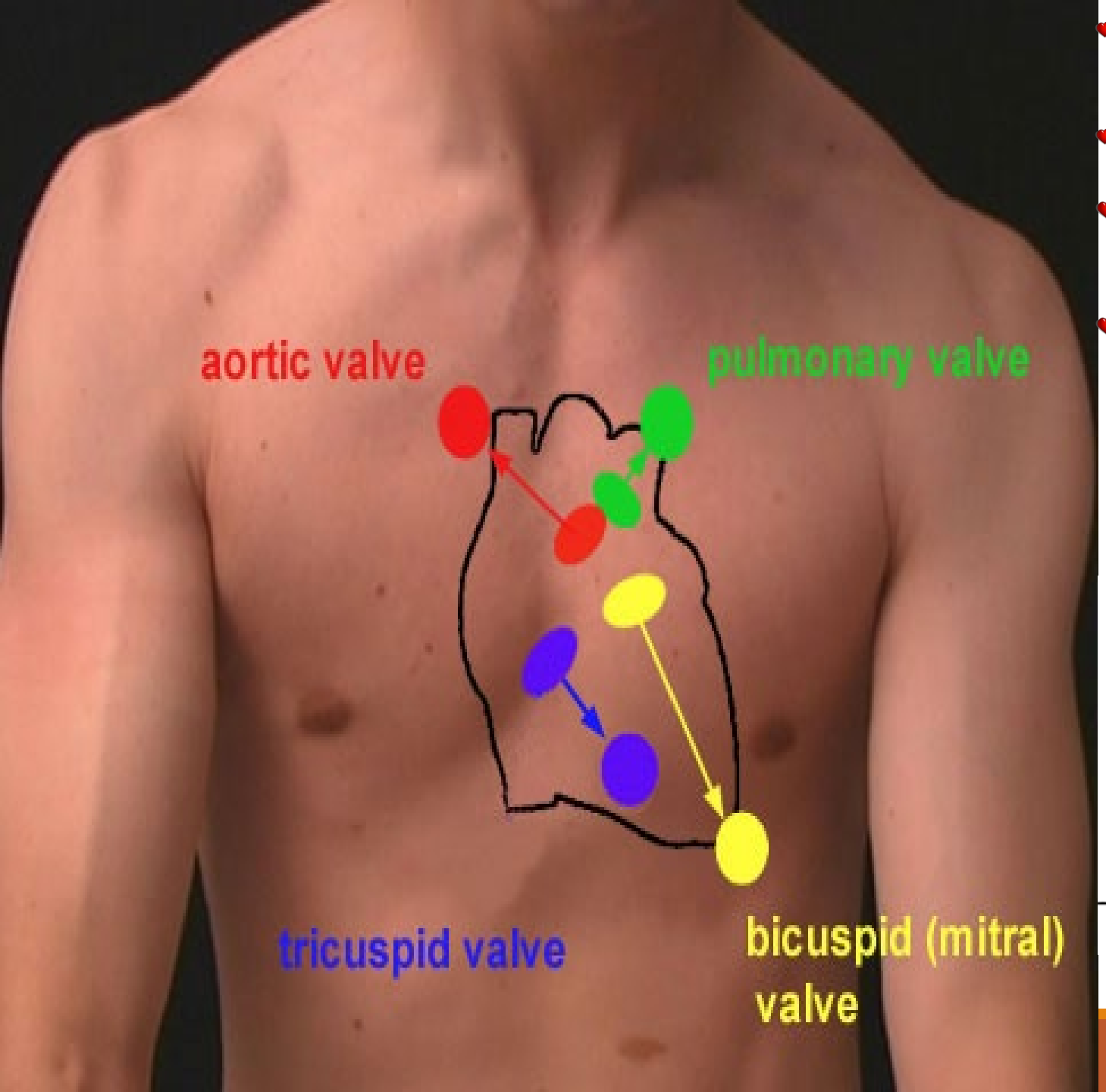
S2= Aortic ,Pulmunary valve then tricuspid mitral valve

S3

- **Right side lower pressure open first , closed second**
- **Left side higher pressure open second , closed first.**







- **BREATH IN[INHALE]** =➔RIGHT SIDE OF HEART LOUDER [SPLIT]
- **BREATH OUT [EXHALE]** ==➔ **LEFT** SIDE OF THE HEART
- **Heart sounds are not caused by opening of the valves**
- **Heart sounds (lub-dup) are associated with closing of heart valves**
  - **First sound occurs as AV valves close and signifies beginning of systole**
  - **Second sound occurs when SL valves close at the beginning of ventricular diastole**

S_1, forms the "lub" of "lub-dub"

S_2, forms the "dub" of "lub-dub"

S1, S2, S3 sound like "Ken-tuck-y" (lub-dub-dub)

Effects of inhalation/expiration

•**Inhalation** pressure causes an **increase in the venous blood return to the right side of the heart.**

- **Therefore, *right-sided murmurs generally increase in intensity with inspiration*.**
- **The increased volume of blood entering the right sided chambers of the heart restricts the amount of blood entering the left sided chambers of the heart.**
- **This causes left-sided murmurs to generally decrease in intensity during inspiration.**

Expiration, the opposite hemodynamic changes occur.

- **This means that left-sided murmurs generally increase in intensity with expiration.**
- **Having the patient lie supine and raising their legs up to a 45 degree angle facilitates an increase in venous return to the right side of the heart producing effects similar to inhalation-increased blood flow.**

S1:

- ♡ **The S1 sound is normally the first heart sound heard.**
- ♡ **The S1 is best heard in the *mitral area*, and corresponds to closure of the mitral and tricuspid (AV) valves.**
- ♡ **A normal S1 is low-pitched and of longer duration than S2.**

S2:

- ♡ **The S2 sound is normally the second sound heard.**
- ♡ **The S2 is best heard over the *aortic area*, and corresponds to closure of the pulmonic and aortic valves.**
- ♡ **A normal S2 is higher-pitched and of shorter duration than S1.**

- **The flow from the ventricles is more forceful than the flow from the atria.**
  - **Therefore, S2 will normally be the louder sound.**

Gradations of Murmurs	(Defined based on use of an acoustic, not a high-fidelity amplified electronic stethoscope)
Grade	**Description**
Grade 1	Very faint, heard only after listener has "tuned in"; may not be heard in all positions. Only heard if the patient "bears down" or performs the Valsalva maneuver.
Grade 2	Quiet, but heard immediately after placing the stethoscope on the chest.
Grade 3	Moderately loud.
Grade 4	Loud, with palpable thrill (i.e., a tremor or vibration felt on palpation)
Grade 5	Very loud, with thrill. May be heard when stethoscope is partly off the chest.
Grade 6	Very loud, with thrill. May be heard with stethoscope entirely off the chest.

More ……..

SOME GENERAL INFO AND REVIEW

Which has a higher compliance, arteries or veins?

Veins

Which contains the larger proportion of blood, arteries or veins?

Veins contain a higher proportion of total blood volume; this is the unstressed volume, a reservoir that can be mobilized in times of need.

The wall of the aorta has one of the highest concentrations of elastin. What does this elastin do for circulation?

It facilitates the Windkessel effect; the heart pushes blood out into the low compliance aorta, which balloons slightly; subsequently, the elastin allows the aorta to force the blood forward into the systemic circulation

What is unique about the capillary bed of the vasculature? Why is that important?

It has the largest cross-sectional area and surface area, which allows for the efficient Exchange of nutrients, water, and gases

What is unique about the pulmonary vasculature compared to the systemic vasculature?

Hypoxia causes vasoconstriction of the pulmonary vasculature. In most organs hypoxia causes vasodilation.

What is the effect of pulmonary hypoxic vasoconstriction?

It shunts blood toward lung segments that are being effectively ventilated

How does flow in the pulmonary circulation relate to flow in the systemic circulation?

They must be equal! While the total amount of blood in each circuit varies at any given time, total flow per unit time through each circuit must be equal.

What is a dromotropic effect?
A change in conduction velocity through a nerve fiber. When talking about the heart, we mean conduction through the AV node with changes in the PR interval
What type of dromotropic effect does the sympathetic nervous system produce?
Positive dromotropic effect (shortening of the PR interval)
Sympathetic stimulation of the heart utilizes what receptor? What is the neurotransmitter used?
*β*1 receptor; norepinephrine (NE) is the neurotransmitter
How does the sympathetic nervous system produce its dromotropic effect?
By increasing the inward Ca2+ current during phase 4, this increase shortens the PR interval, thereby increasing the overall heart rate
What type of dromotropic effect does the parasympathetic nervous system produce?
Negative dromotropic effect (lengthening of the PR interval)
Parasympathetic stimulation of the heart utilizes what receptor? What is the neurotransmitter used?
Muscarinic receptor; acetylcholine (ACh) is the neurotransmitter
How does the parasympathetic system produce its dromotropic effect?
It decreases the inward Ca2+ current and increases the outward K+ current; this decreased conduction velocity increases the PR interval, slowing the heart rate
How does dromotropy differ from chronotropy?
They are intimately related, but chronotropy refers specifically to *heart rate* as determined by the SA node; dromotropy more specifically refers to AV nodal conduction

Where do pacemaker potentials occur normally?
1. Sinoatrial (SA) node
2. Atrioventricular (AV) node
3. His-Purkinje systems

What is the normal pacemaker of the heart?
The SA node

What is the normal pacing rate of the SA node?
60 to 100 potentials/min

What are the latent pacemakers in the heart?
AV node and His-Purkinje system

When might latent pacemakers take over for the main pacemaker?
Either when the SA node is suppressed or if conduction is blocked

What are the average pacing rates of the AV node and His-Purkinje system?
Average pacing rates are 45 and 30 beats/min, respectively

What is conduction velocity?

The rate at which an electrical impulse propagates through cardiac tissue

Describe the anatomical flow of electrical propagation in the heart:

SA node generates an AP, this flows through the right atria (and to the left atria via Bachmann bundle) to the AV node. There it is delayed briefly before flowing through the His-Purkinje system into both ventricles concurrently.

What does conduction velocity depend on?

The magnitude of the inward current due to the influx of ions during phase 0 of the cardiac action potential

Where is conduction velocity the fastest?

Purkinje system

Where is conduction velocity the slowest?

AV node

What does the difference in conduction time between the AV node and the Purkinje system allow the heart to do?

The delay allows the ventricle to fill completely by accepting the “atrial kick”

What can happen if conduction velocity through the AV node is increased?

Ventricular filling can be compromised

In contrast to the neuromuscular junction of striated muscle, what is the stimulus for cardiac contraction?
Pacemaker potentials
What is a sarcomere?
Contractile unit of a myocardial cell
What is the role of the intercalated disk?
Maintains cell-to-cell cohesion and houses the gap junctions between cells
What is the role of the gap junction?
Provides a low-resistance path between cells, which allows for the rapid propagation of electrical impulses
What is the role of the T tubule?
Rapidly carries action potentials from the cell surface to the myocardial cell interior
What is the role of the sarcoplasmic reticulum (SR)?
Stores and releases Ca^{2+} for myocardial cell excitation-contraction coupling

What occurs in excitation-contraction coupling within the myocardium once the action potential enters the cell via the T tubules?

Ca^{2+} enters the cell from the extracellular fluid (ECF), creating an inward Ca^{2+} current

↓

Influx of Ca^{2+} causes the SR to release its stores of Ca^{2+}, further increasing the intracellular $[Ca^{2+}]$ (Calcium-induced calcium release)

↓

Ca^{2+} binds to troponin C molecules, which displaces the tropomyosin protein allowing the actin and myosin to bind, thereby generating contraction

↓

The SR reaccumulates the Ca^{2+}, which causes the myocardial cell to relax

What influences the amount of Ca^{2+} released by the SR during myocardial contraction?
Amount of Ca^{2+} stored in the SR and the size of the inward Ca^{2+} current
The magnitude of contraction for a myocardial cell is proportional to what variable?
The intracellular [Ca^{2+}]
Is reuptake of Ca^{2+} by the SR during relaxation of the myocardium an active or passive process?
It's an active process mediated by Ca^{2+}-ATPase pump
What is cardiac oxygen consumption related to?
It is directly related to the amount of tension developed in the cardiac muscle
What factors can increase cardiac oxygen consumption?
1. Increased afterload
2. Increased contractility
3. Increased heart rate (HR)
4. Hypertrophy of the cardiac muscle

(Note: All of these increase the amount of *work* that the cardiac muscle has to do.)

- **Pacemaker cells have no stable resting membrane potential.**
- **Their special hyperpolarization-activated cation channels (funny channels) ensure a spontaneous new depolarization at the end of each repolarization and are responsible for automaticity of the heart conduction system! In sympathetic stimulation, more I_f channels open, increasing the heart rate.**
- **Upstroke and depolarization of a pacemaker cell are caused by the opening of voltage-activated L-type calcium channels.**
- **In other muscle cells and neurons, upstroke and depolarization are caused by fast sodium channels!**
- **The duration of action potentials differs in the various structures of the conduction system and increases from the sinus node to the Purkinje fibers!**

What is contractility?
The ability of a muscle fiber to develop a force at a given muscle length
What is another term for contractility?
Inotropy
Can we alter the inotropic state of skeletal muscle?
No, it is a unique characteristic of cardiac muscle
What can be used as an estimate of contractility?
Ejection fraction (EF), which gives us a measure of how much blood is pushed out of the ventricle with each contraction

What is the normal range of EF?

The normal range of EF ≈ 55% to 80%

What is a positive (negative) inotropic agent?

Anything that causes an increase (decrease) in contractility

Generally speaking, what are some positive inotropes?

- Sympathetic stimulation
- Increased intracellular Ca2+
- Decreased extracellular Na+
- Cardiac glycosides

What are some negative inotropes?

- Parasympathetic stimulation
- β1-blockade
- Acidosis
- Hypoxia
- Hypercapnia

How does sympathetic stimulation increase contractility?

By increasing inward Ca2+ current during phase 2; G-proteins phosphorylate phospholamban proteins. This increases SR Ca2+ release providing more Ca2+ for excitation-contraction coupling.

What receptor does the sympathetic nervous system use to increase contractility?
β_1 receptors (Note: the same receptor used for dromotropic and chronotropic stimulation)

How does parasympathetic stimulation decrease contractility?
Muscarinic receptors are stimulated by ACh to decrease the inward Ca^{+} current during phase 2 of cardiac depolarization

How do cardiac glycosides increase contractility?
Myocardial cell membrane Na^{+}-K^{+}-ATPase is inhibited, which diminishes the Na^{+} gradient across the cell membrane. This increased intracellular [Na^{+}] decreases Ca^{2+} efflux by the Na^{+} -Ca^{2+} exchange mechanism thereby increasing intracellular Ca^{2+}.

Clinically, what is the equivalent to preload?
Ventricular EDV, which approximates the degree of myocyte stretch

What effect do venodilators have on preload?
They decrease it by allowing for pooling of venous blood, decreasing EDV

What are some things that can cause an increase in preload?
- Increased blood volume
- Sympathetic stimulation
- Exercise (slight increase)

What is afterload equivalent to?
Diastolic arterial pressure

What is afterload proportional to?
Peripheral resistance

What effect do vasodilators have on afterload?
Decrease it

What can increase the contractility of the myocardium?

- Pharmacologic stimulants
- Sympathetic stimulation
- Circulating catecholamines (epinephrine)
- Abrupt increase in afterload (Anrep effect)
- Increased HR (Bowditch effect)

What can decrease the contractility of the myocardium?

- Pharmacologic depressants
- Parasympathetic stimulation
- Loss of myocardium
- Heart failure

What event does the first heart sound (S1) correspond to?
Mitral and tricuspid valve closure
What event does the second heart sound (S2) correspond to?
Aortic and pulmonic valve closure
What is a *split* S2?
When the aortic valve closes before the pulmonic valve
Is this split considered physiologic?
Yes, it can be. It is often called “the physiologic split.”
What maneuver enhances the physiologic split?
Inspiration. The increased preload, leads to a delayed pulmonic closure, thereby widening the S2 split.
What are the potentially pathological heart sounds (gallops)?
S3 and S4
In what instances are the heart sounds not pathological?
S3: normal in children, and pregnant women
S4: can be normal in kids and athletes, but standard mantra says “always pathologic”

Describe in words, the S3 and S4 heart sounds:
S3: immediately following isovolumetric relaxation, the mitral valve opens and blood rushes into a dilated ventricle; like water into a grocery bag
S4: with atrial systole, the atria squeezes blood into a rigid ventricle (often secondary to hypertrophy), that rigidity is appreciated with the stethoscope as an S4

What pathology are the abnormal heart sounds associated with?
S3: dilated congestive heart failure (CHF)
S4: hypertrophic ventricle

When would you hear the abnormal heart sounds?
S3: last third of diastole
S4: just before S1 (during atrial systole)

What percentage of cardiac output is directed to the following circulations?

- **Brain**

4%

- **Heart**

15%

- **Kidneys**

20%

- **Gut**

25%

What is autoregulation?

Mechanism by which local vascular circuits are altered to meet the demands of specific tissues

What organs exhibit autoregulation?

Brain, heart, and kidney

What is active hyperemia?

Blood flow to the organ is proportional to the metabolic activity of the organ

What is reactive hyperemia?

Transient increase in blood flow to an organ after it has undergone a brief period of arterial occlusion (e.g., ischemia)

What factors can influence autoregulatory set-points in the following locations?

Brain

Local metabolic factors: PCO_2; a rising PCO_2 causes cerebral vasodilation

Heart

Local metabolic factors: hypoxia, adenosine, and nitrous oxide (NO)

Kidney

Myogenic and tubuloglomerular feedback

Name		Definition	Site	Direction of flow	Activation phase (affected tissue)
Calcium channels	**Voltage-gated L-type calcium channel** (i_{Ca})	Ca^{2+} channels on the surface of myocytes, which open at about -40 mV and allow intracellular calcium influx	Cell membrane	Extracellular calcium → cytoplasm	Plateau phase (myocardium) and raising phase (SV node)
	Ryanodine receptor	Ca^{2+} channel in the membrane of the SR that opens after binding of Ca^{2+} (referred to as calcium-induced Ca^{2+} release)	Membrane of SR	Ca^{2+} from SR → cytoplasm	Plateau phase (myocardium)
Calcium pumps	**SERCA** (sarcoplasmic Ca^{2+}-ATPase)	Ca^{2+} pumps and exchanger that remove Ca^{2+} from the cytosol, thereby terminating a contraction	Membrane of SR	Ca^{2+} in cytoplasm→ SR	Plateau phase (myocardium)
	Na^{+}/Ca^{2+}-exchanger		Cell membrane	Ca^{2+} in cytoplasm→ extracellular	

Cardiac channels

- The action potentials of the pacemaker centers are transmitted to the cells of the myocardium via the cardiac conduction system, thereby depolarizing the cells (electromechanical coupling).
- As a result, voltage-activated calcium channels open, causing calcium ions to flow into the cardiomyocytes.
- Calcium binds to regulatory proteins of myofilaments(troponin) and allows interaction of actin and myosin.
- The muscle cell contracts.
- The exact course of the molecular interaction of actin and myosin (filament sliding theory) is dealt with in the basics of muscle tissue.
- **Calcium channels and calcium pumps**

Other cation channels
All are located in the cell membrane.

Name		Definition	Ion and direction of flow	Activation phase (affected tissue)
Funny channels (HCN, I_f)		Nonselective cation channels (e.g., for Na^+, K^+) in pacemaker cells that open as the membrane potential becomes more negative (hyperpolarized)	Cations extracellular → intracellular	Raising phase (sinus node)
Fast sodium channels (I_{Na})		Na^+ channels that rapidly open and close following depolarization	Na^+ extracellular → intracellular	Depolarization(myocardium)
Potassium channels	**Inward rectifier K^+channels**	K^+ channels that open below −70 mV and stabilize the resting potential of the myocardiocytes by outflow of K^+	K^+ intracellular → extracellular	Resting potential(myocardium > sinus node)
	Delayed rectifier K^+channels(I_{Kr} & I_{Ks})	K^+ channels that can be rapidly (I_{Kr}) or slowly (I_{Ks}) activated upon depolarization	K^+ intracellular → extracellular	Repolarization (sinus node and myocardium)

Cardiac action potential	ardial action potential (myocardium bundle of His Purkinje fibers)	Pacemaker action potential (SA node and AV node)
Phase 0 (Upstroke and depolarization)	•An action potential from a pacemaker cell or adjacent cardiomyocyte causes the transmembrane potential (TMP) to rise above −90 mV •Fast voltage-gated Na^+ channels open at -65 mV → rapid Na^+ influx into the cell → TMP rises further until slightly above 0 mV (overshoot)	•At TMP -40 mV (threshold potential of pacemaker cells): L-type Ca^{2+} channels open, TMP raises to +40 mV (overshoot**/upstroke**) •**No rapid depolarization** phase because fast voltage-gated Na^+ channels are inactivated in pacemaker cells → results in slower conduction velocity between atria and ventricles.
Phase 1 (Early repolarization)	•Voltage-gated Na^+ channels close •Transient K^+ channels start to open (outward flow of K^+ returns TMP to 0 mV)	•**Absent**
Phase 2 (Plateau phase)	•K^+ efflux through delayed rectifier K^+ channels and Ca^{2+} influx through voltage-gated L-type Ca^{2+} channels, which triggers Ca^{2+} release from the sarcoplasmic reticulum (i.e., Ca^{2+}-induced Ca^{2+} release) and contraction of the myocyte •TMP is maintained at a plateau just below 0 mV	•**Absent**

Phase 3 (Repolarization)	•Rapid repolarization due to: • Inactivation of voltage-gated Ca^{2+} channels • K^+ efflux through delayed rectifier K^+ channels continues: persistent outflow of K^+ exceeds Ca^{2+} inflow and brings TMP back to -90 mV •The sarcolemmal Na^+-Ca^{2+} exchanger, Ca^{2+}-ATPase, and Na^+-K^+-ATPaserestore normal transmembrane ionic concentration gradients (Na^+ and Ca^{2+} ions return to extracellular space, K^+ to intracellular space)	•Closure of voltage-gated Ca^{2+} channels and •Opening of delayed rectifier K^+ channels → K^+ efflux (TMP returns to -60 mV)
Phase 4 (Resting phase)	•Resting membrane potential stable at -90 mV due to a constant outward leak of K^+ through inward rectifier channels •Na^+ and Ca^{2+} channels closed	•**No resting phase** (unstable membrane potential) • Gradual Na^+/K^+ entry via funny channels I_f (referred to as the funny currentor **pacemaker current**) → slow spontaneous depolarization (TMP raises above -60 mV) → no external action potential needed (**automaticity of SA and AV nodes**) • At TMP -50 mV: T-type Ca^{2+} channels open. Shortly before reaching the threshold potential (-40mV), L-type Ca^{2+} channel begin to open (see phase 0)