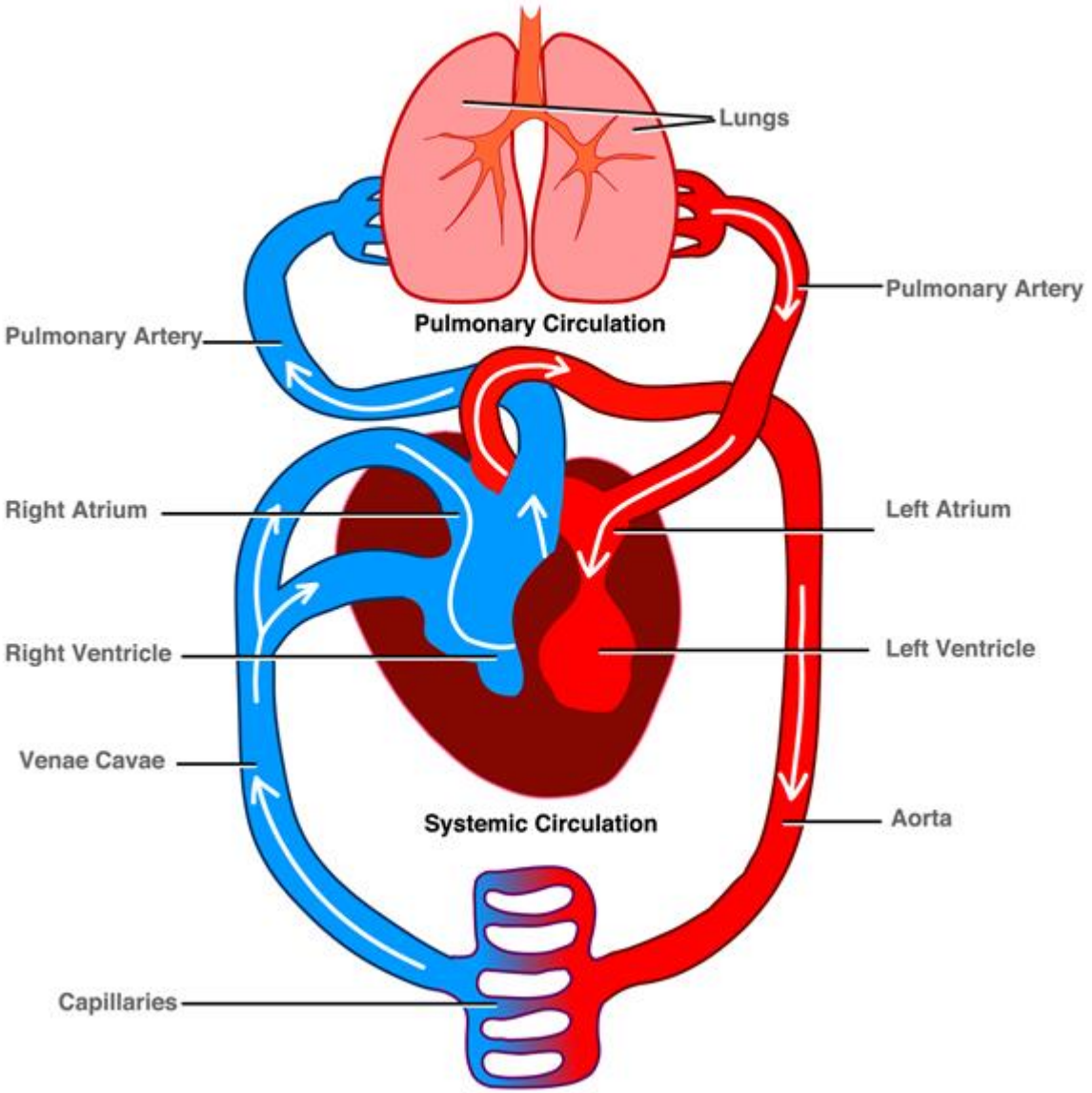
The Cardiovascular System



Cardio vascular System

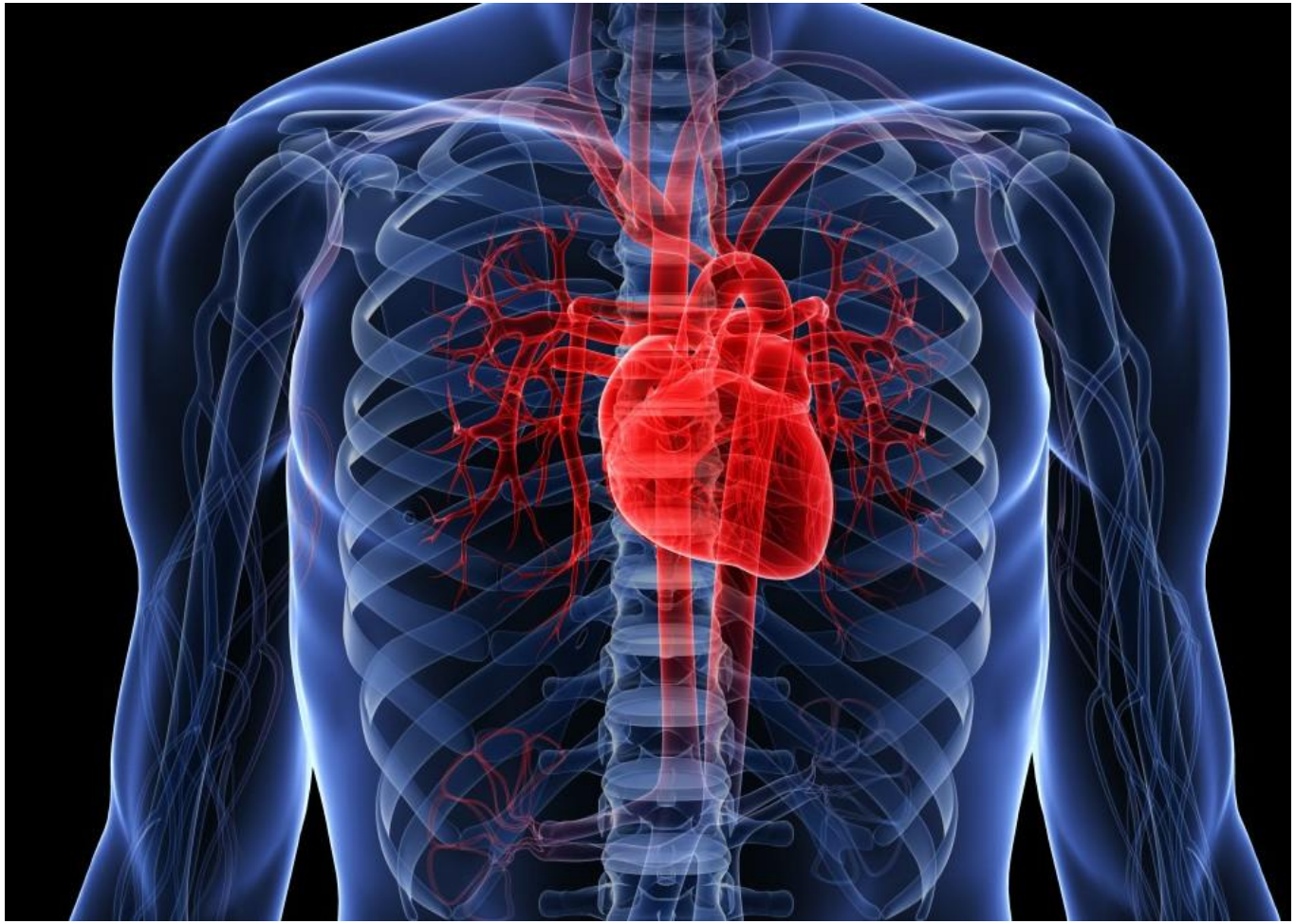
Comprise of :-

- Heart – **Pumps or pushes** blood through body
- Blood Vessels – Like **tubes** - through which blood flows
- Blood – Fluid/liquid which **carries** oxygen, food and waste products

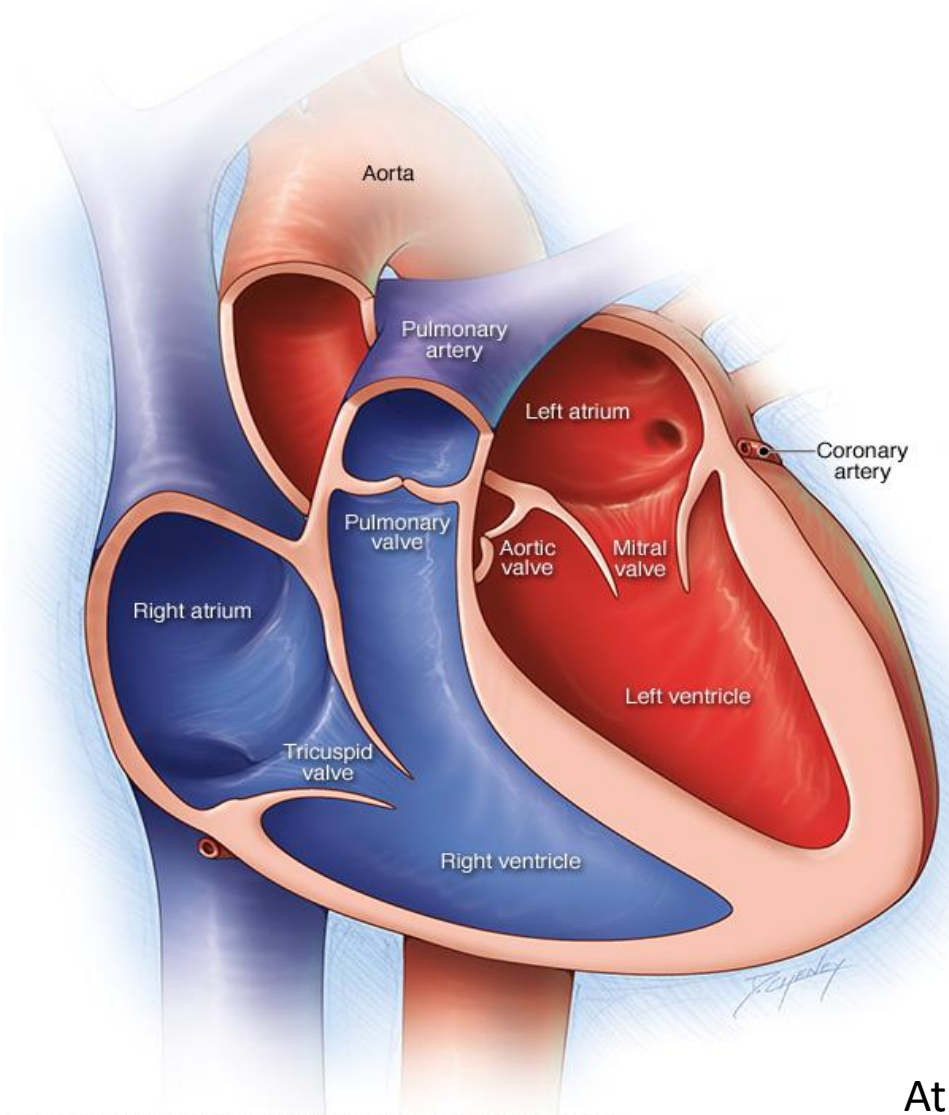
Blood = transport vehicle
Heart = pump
Blood vessels = network of tubes

- Main function of CVS: Transportation
  - To **delivers oxygen**, nutrients, hormones, and other important substances to cells and organs in the body.
  - To **remove metabolic end products** from tissue

HEART



Structure of the heart



- **Cone** shaped muscular organ
- 4 Chambers - 2 upper and 2 lower

Upper chambers-

1. Right Atrium- and
2. Left Atrium,

Lower chambers -

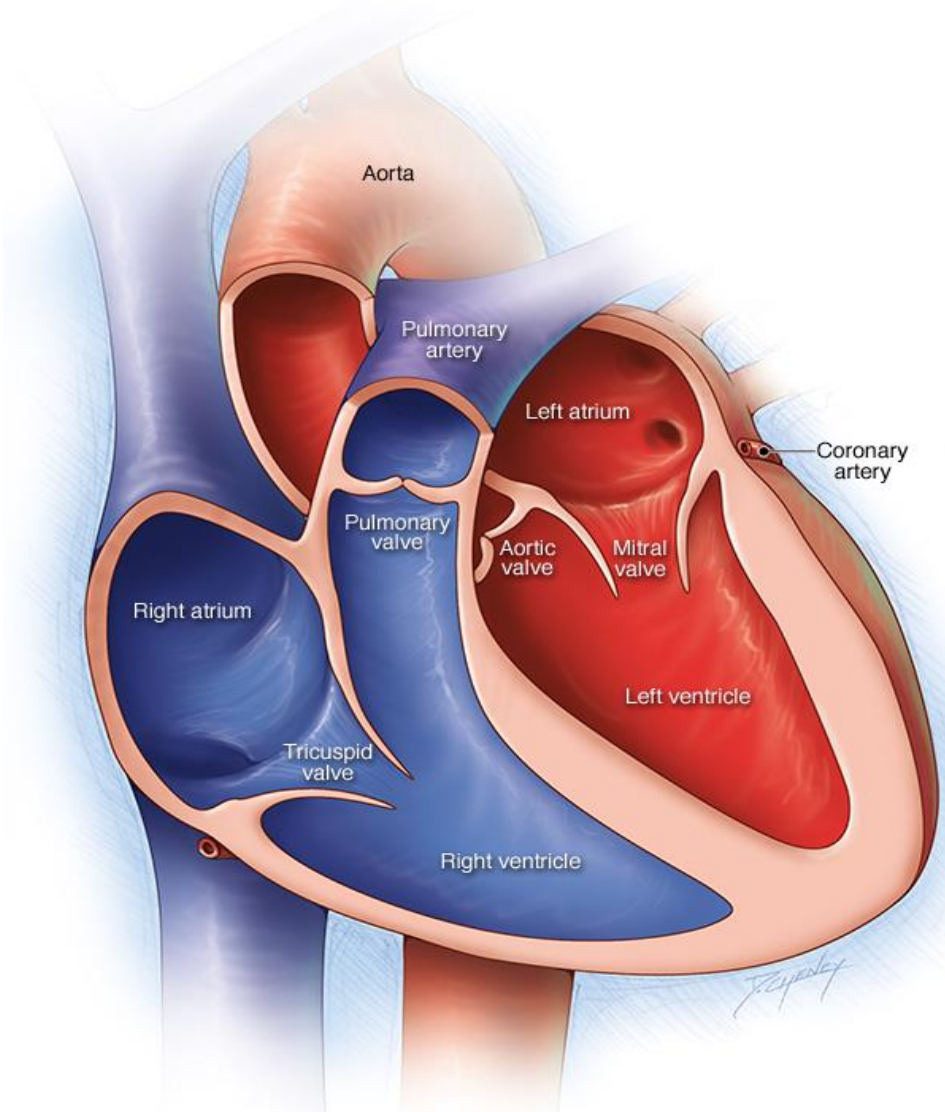
1. Right Ventricle
2. Left Ventricle

Atria – filling chamber , thin wall.

Ventricles- empting chambers , thick wall

Atrium=entryway

Structure of the heart

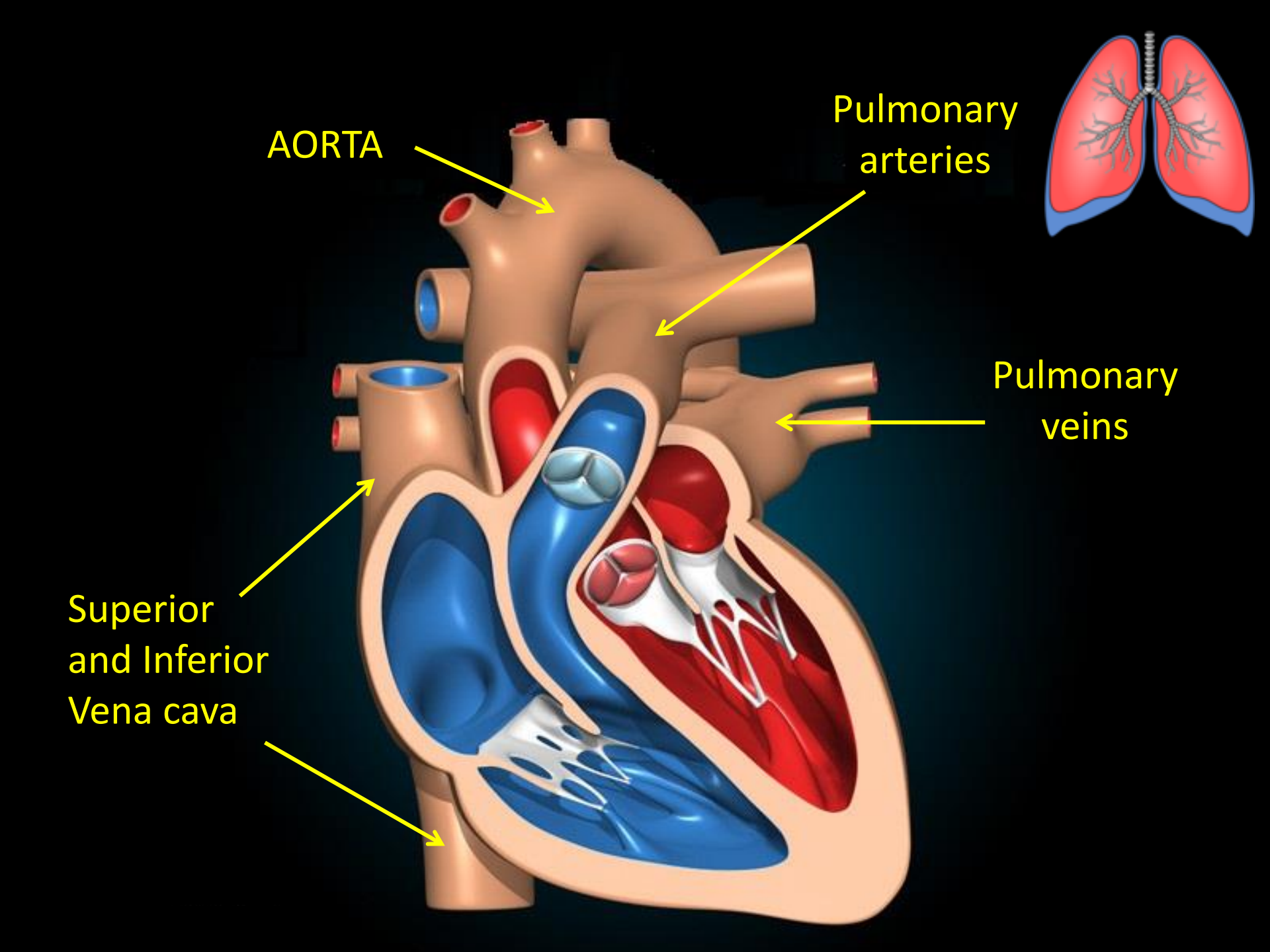


- **Septum** – **prevent** oxygenated and deoxygenated **blood mixing** between chambers.

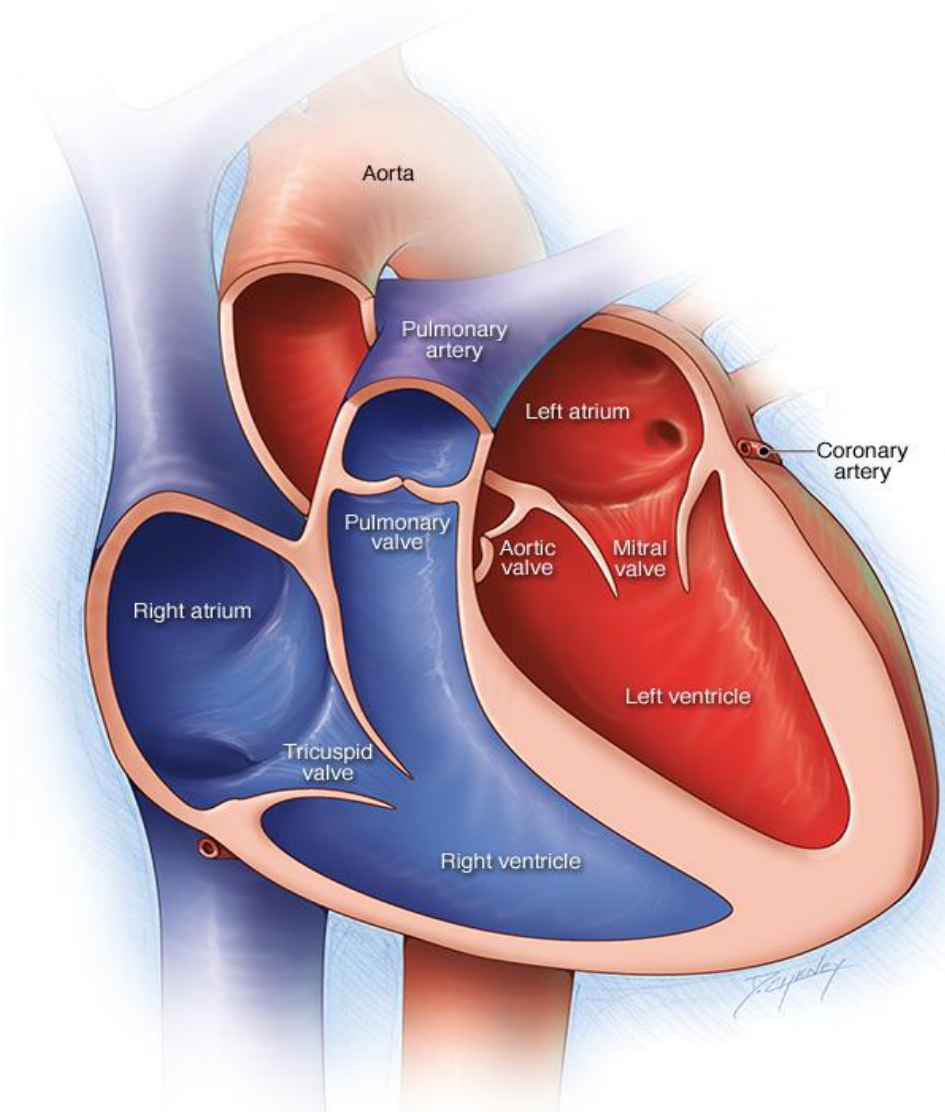
  1. Atria are separated by **interatrial septum**

  2. Ventricles are separated by **Interventricular septum**

- **Blood vessels –**
  1. **Vanacava**
  2. **Pulmonary artery**
  3. **Aorta**
  4. **Pulmonary veins**


AORTA
Pulmonary arteries
Pulmonary veins
Superior and Inferior Vena cava

Structure of the heart

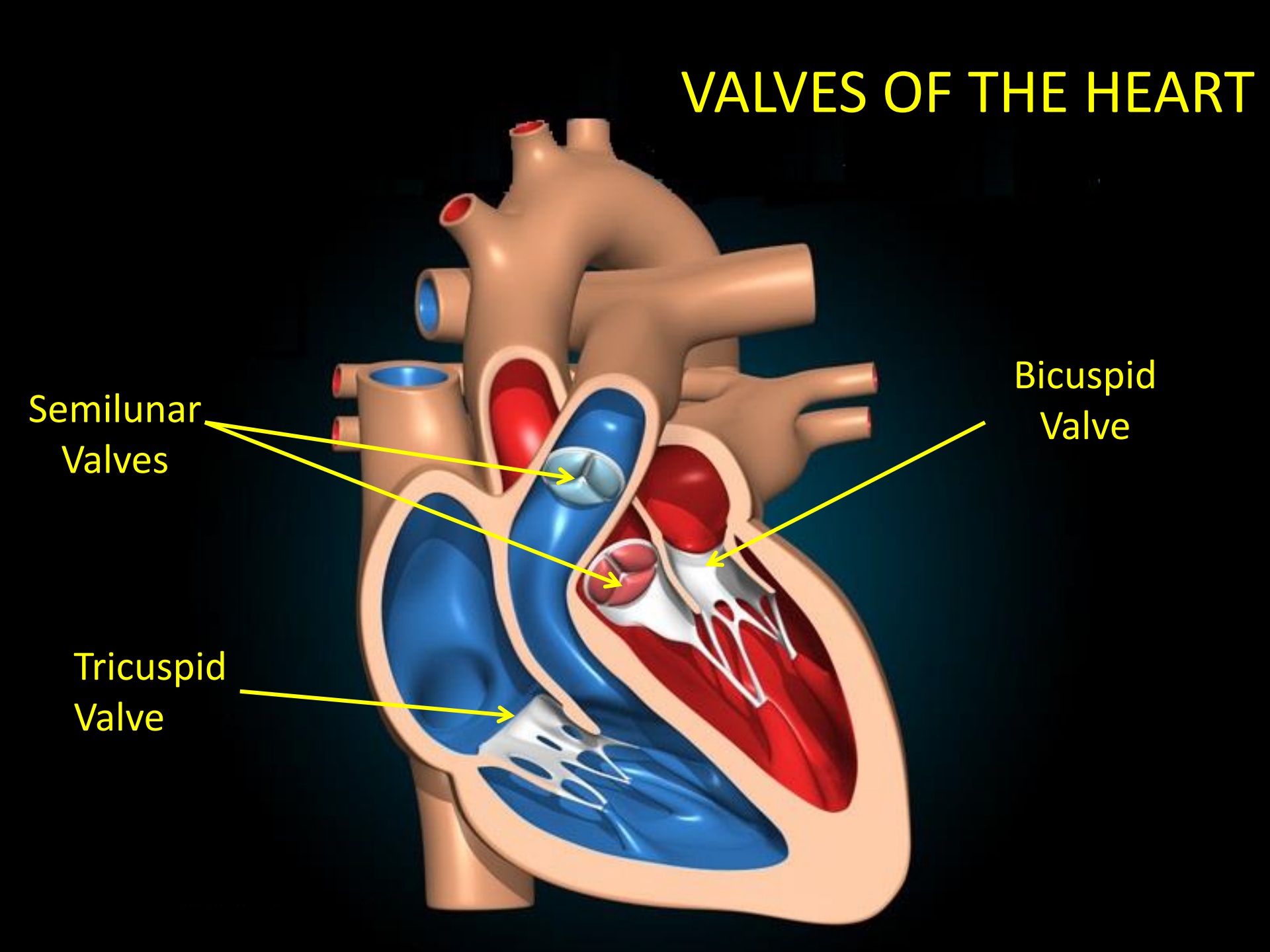


Valves- prevent backward flow of **blood**.

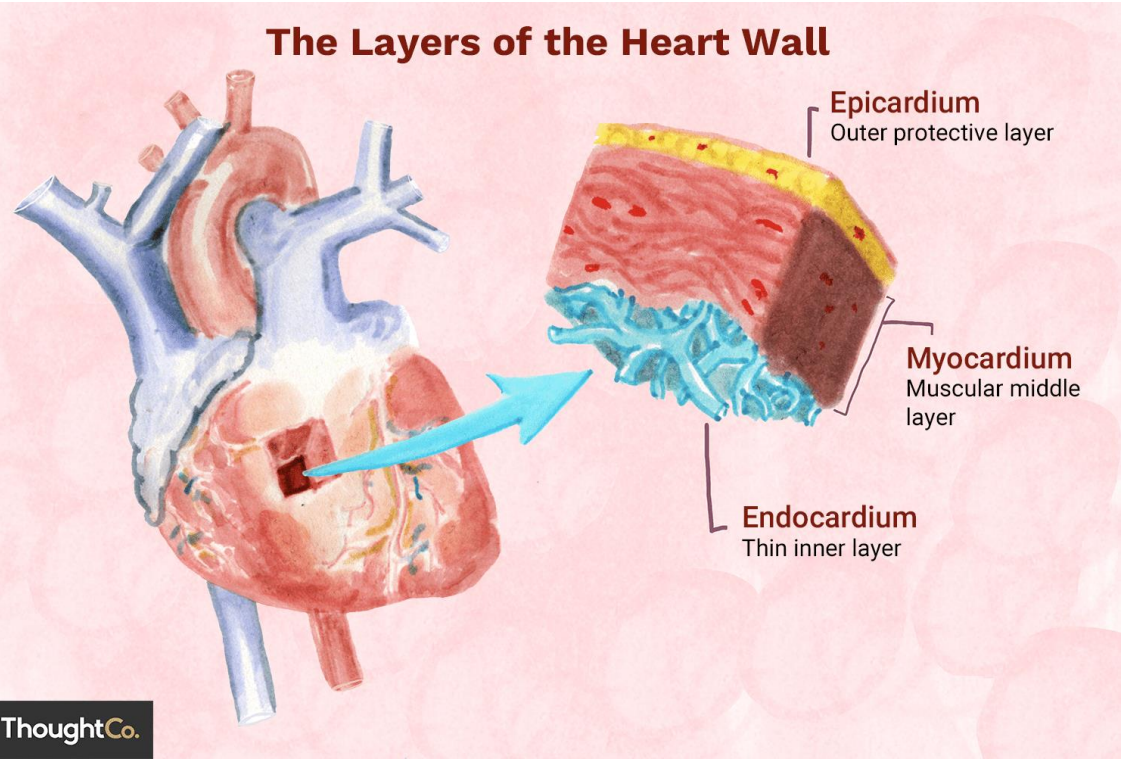
1. **Atrium and ventricle** are **separated** by **atrioventricular valve.** (e.g prevent blood flow from ventricle to atrium) .
    1. Right Side- **Tricuspide** Valve- have **three** cups
    2. Left Side- **Mitral** Valve- has **two** cups

2. **Blood vessel valve (semilunar valve)**:-
    1. **Pulmonary valve**
    2. **Aortic valve**

VALVES OF THE HEART



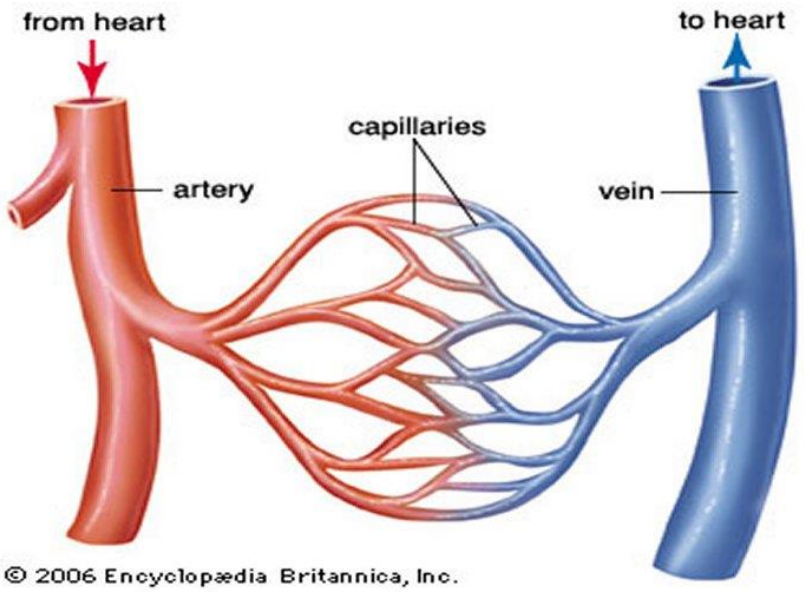
Structure of the heart



- Heart is Made up of 3 Layers -
  1. Endocardium,
  2. Myocardium,
  3. Epicardium

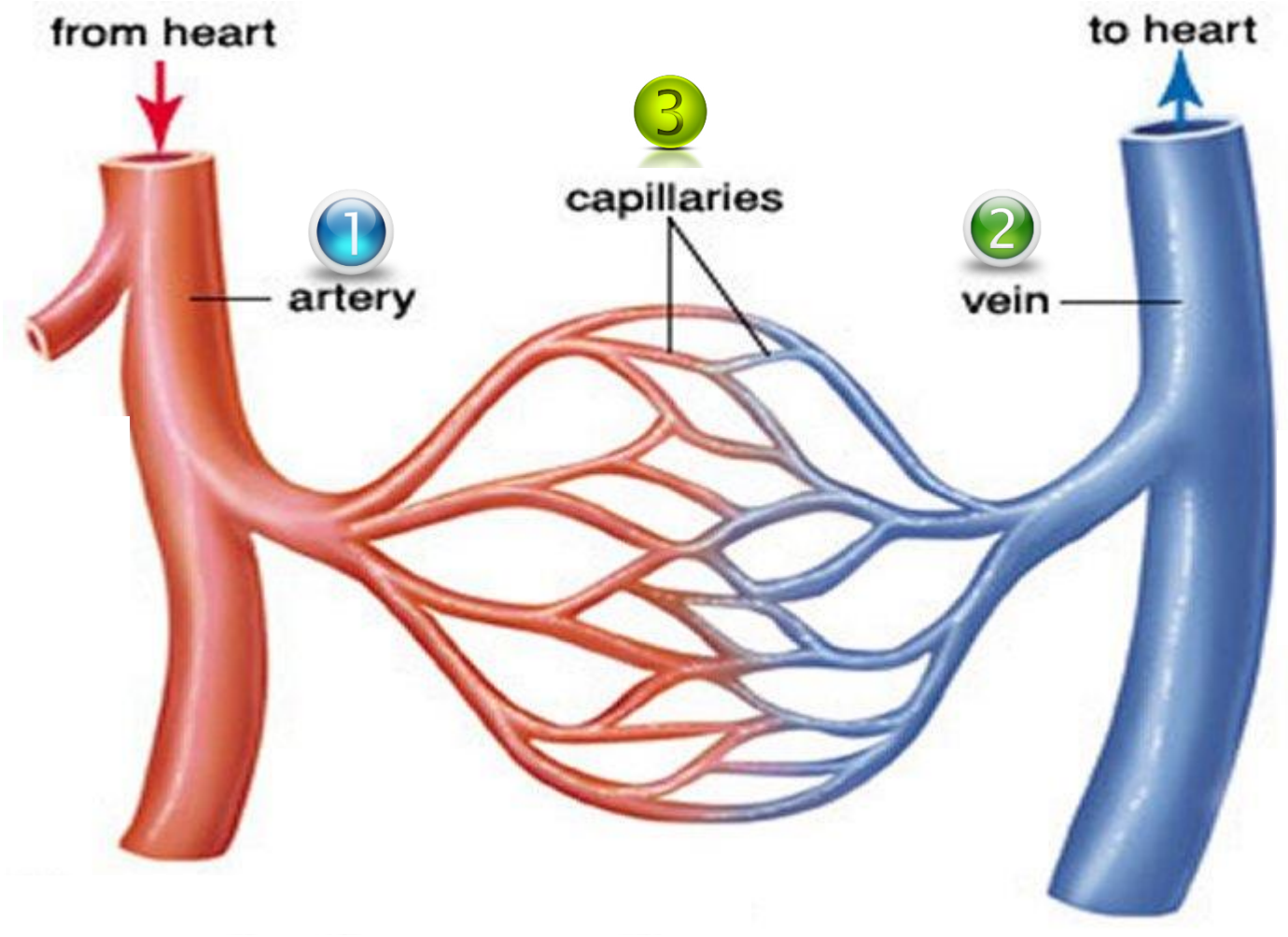
Blood Vessels – 3 types

- **A closed system of blood vessels:** These vessels include:
  - **Arteries:** Vessels that carry blood **Away** from the heart.
  - **Veins:** Vessels that bring blood **back** to the heart.
  - **Capillaries:** Tiny vessels that **branch off from arteries** to deliver blood to all body tissues*.



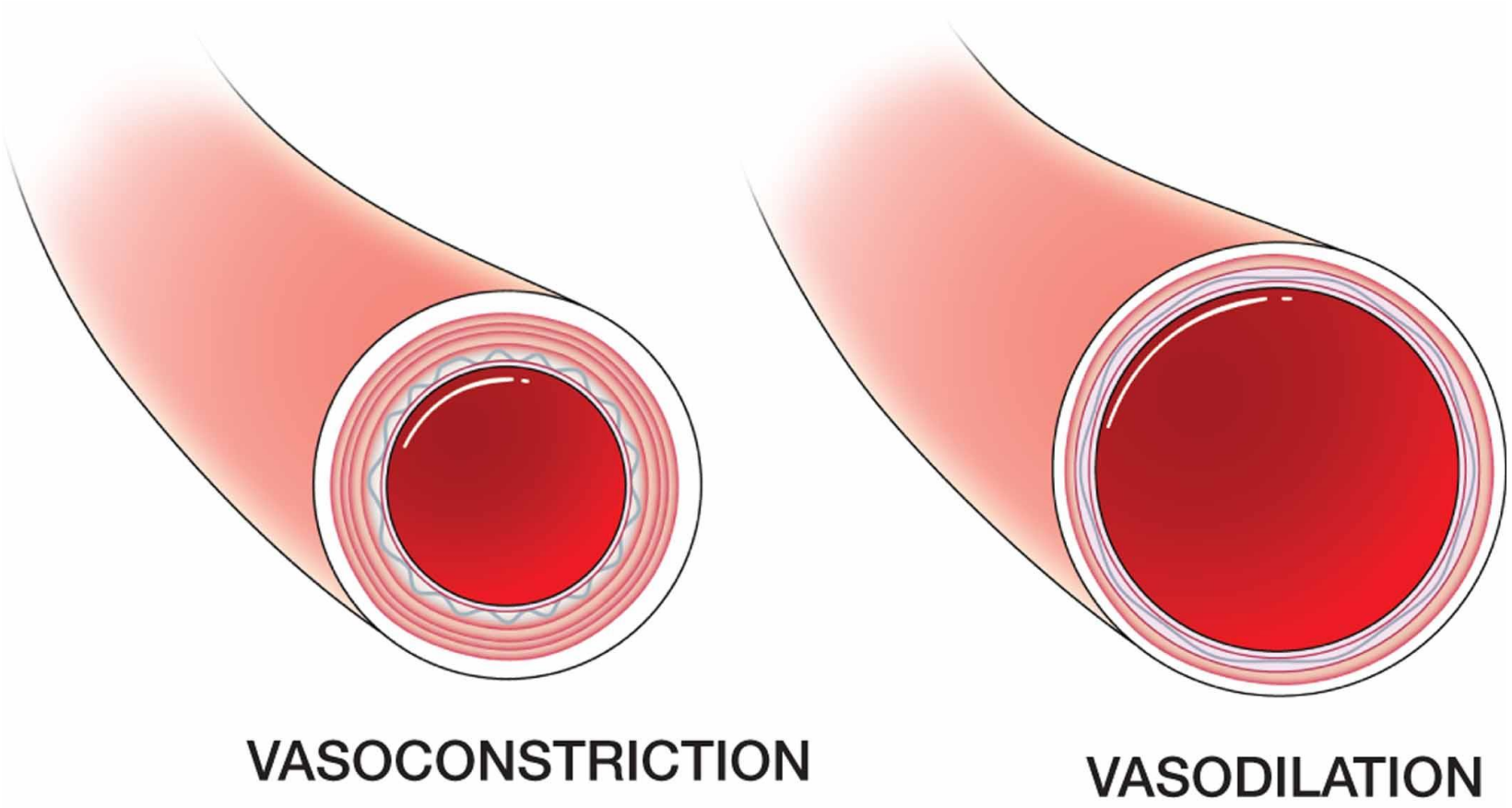
*PubMed Central

Blood Vessels – 3 types

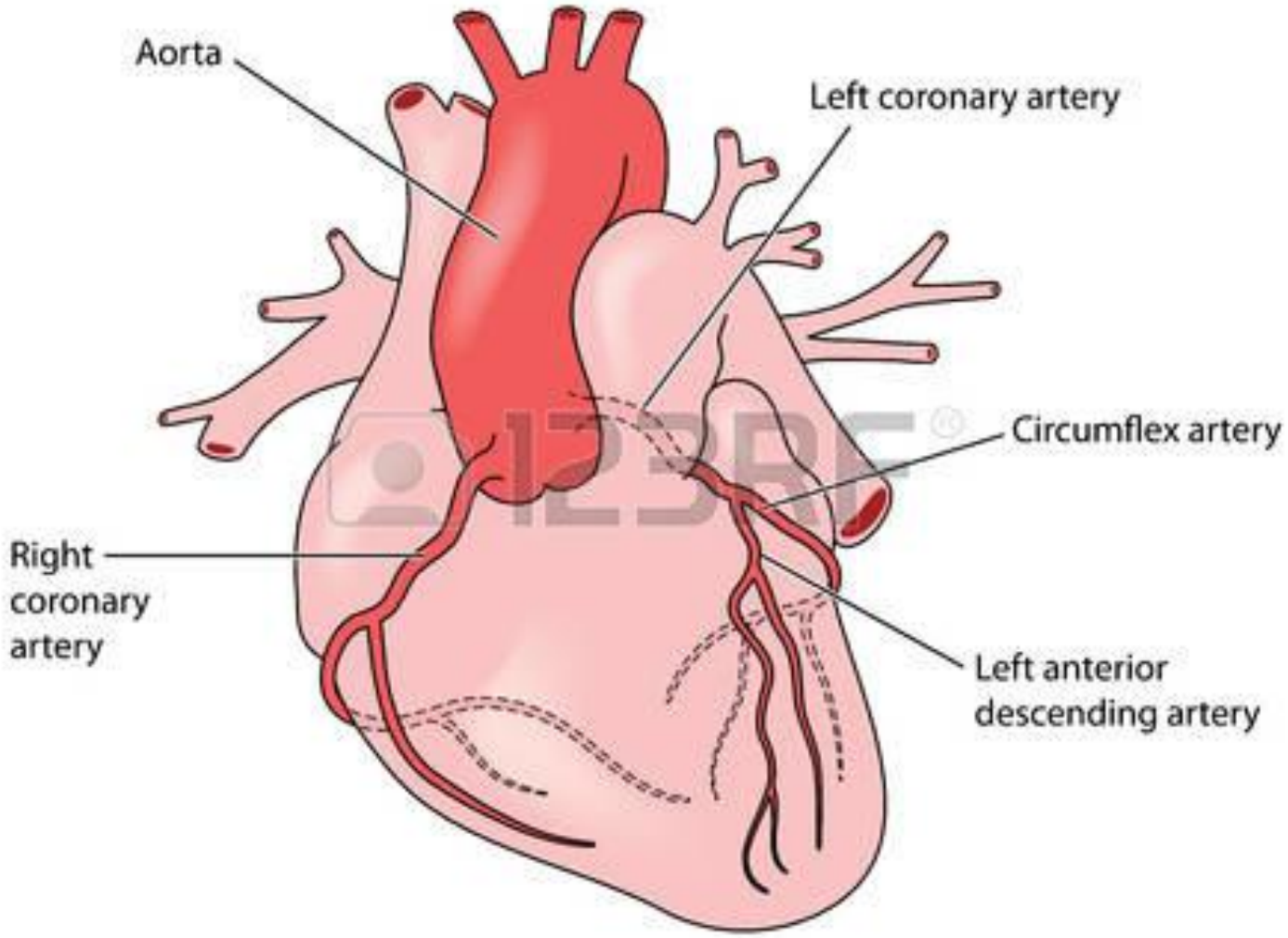


Vaso -constriction

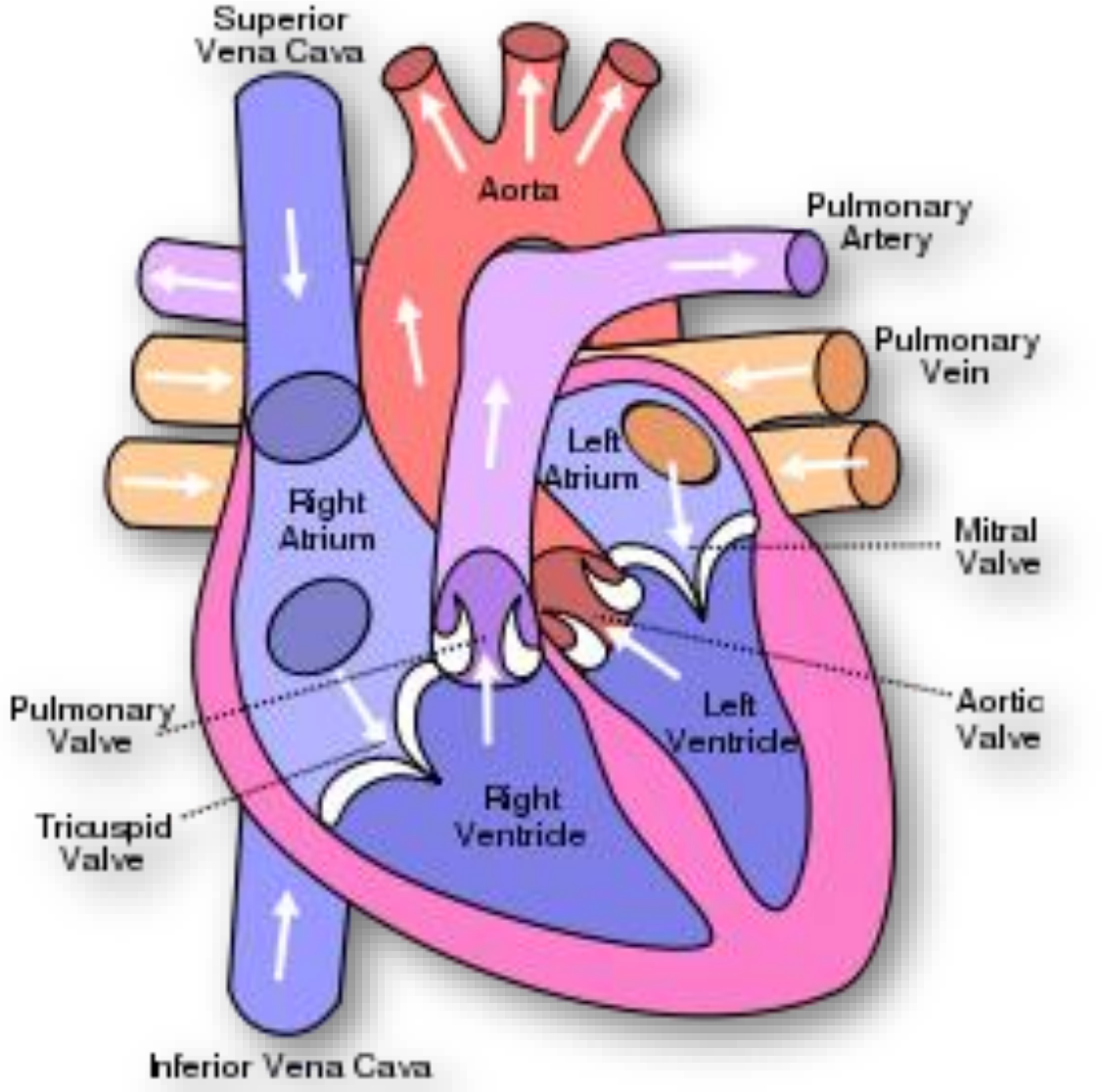
Vaso -Dilatation



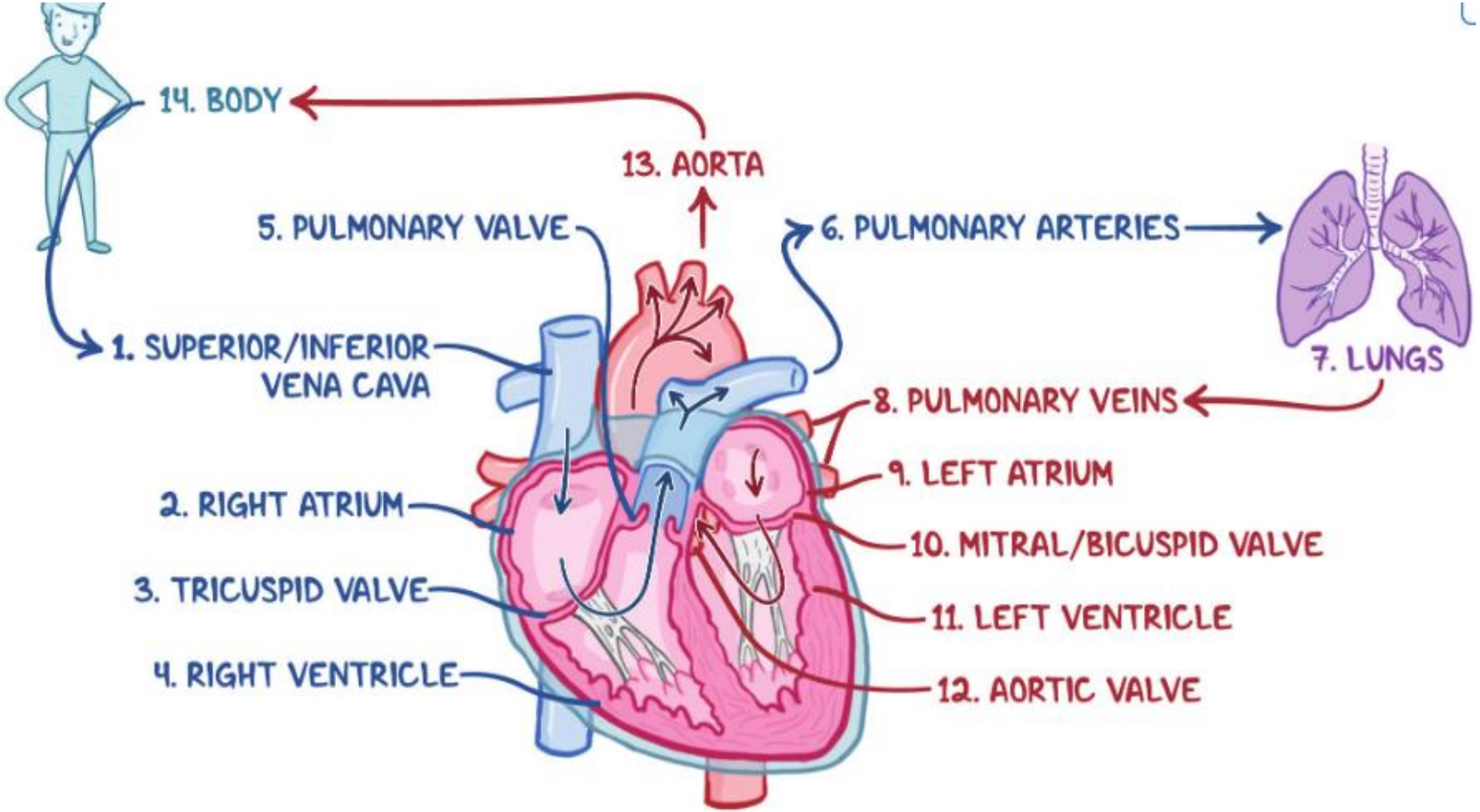
Coronary arteries



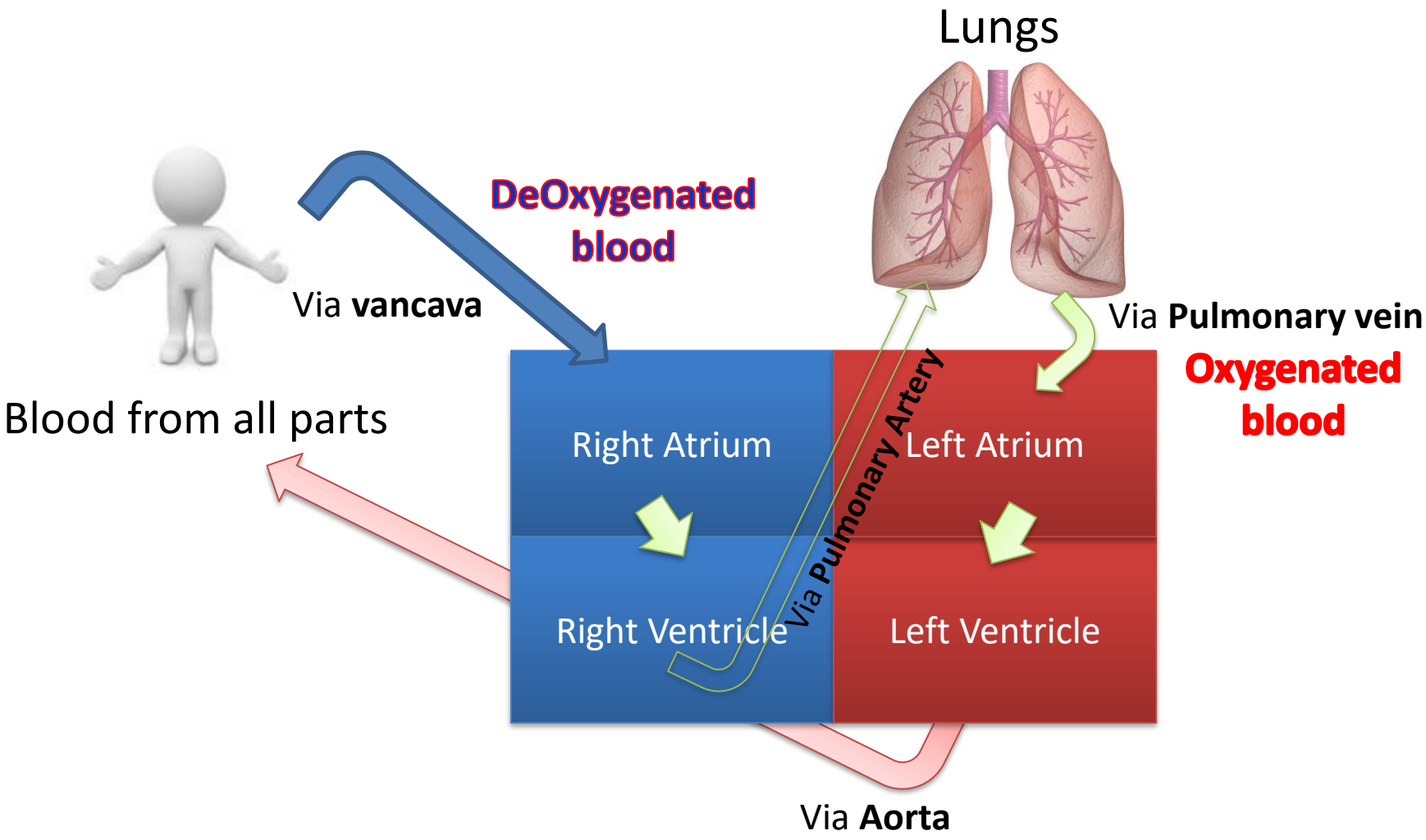
Revision - Structure of the heart



Functioning of the HEART

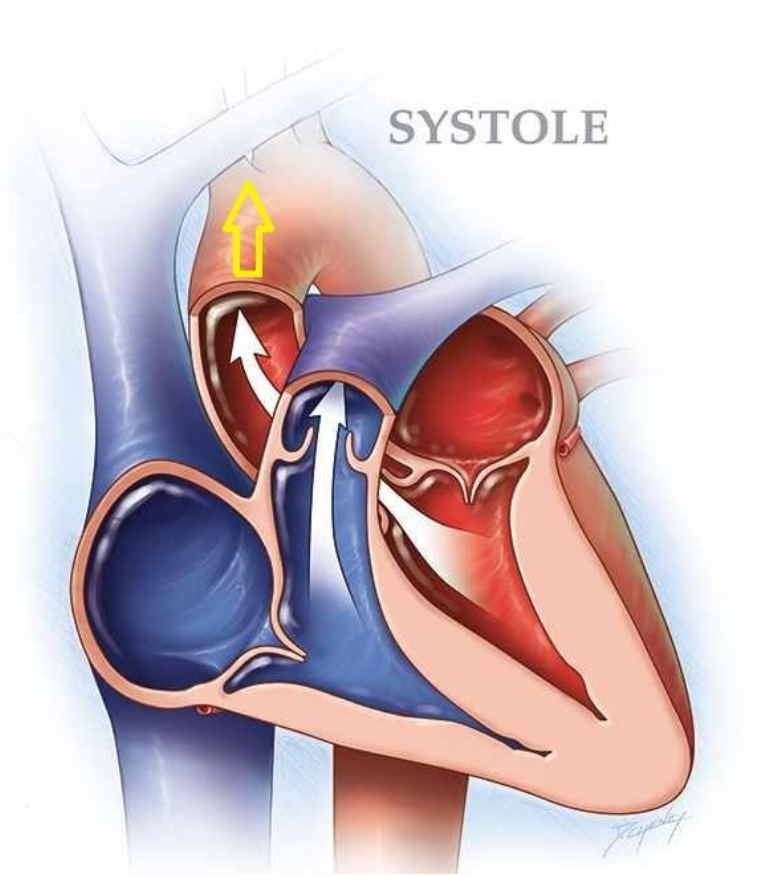


Functioning of the HEART

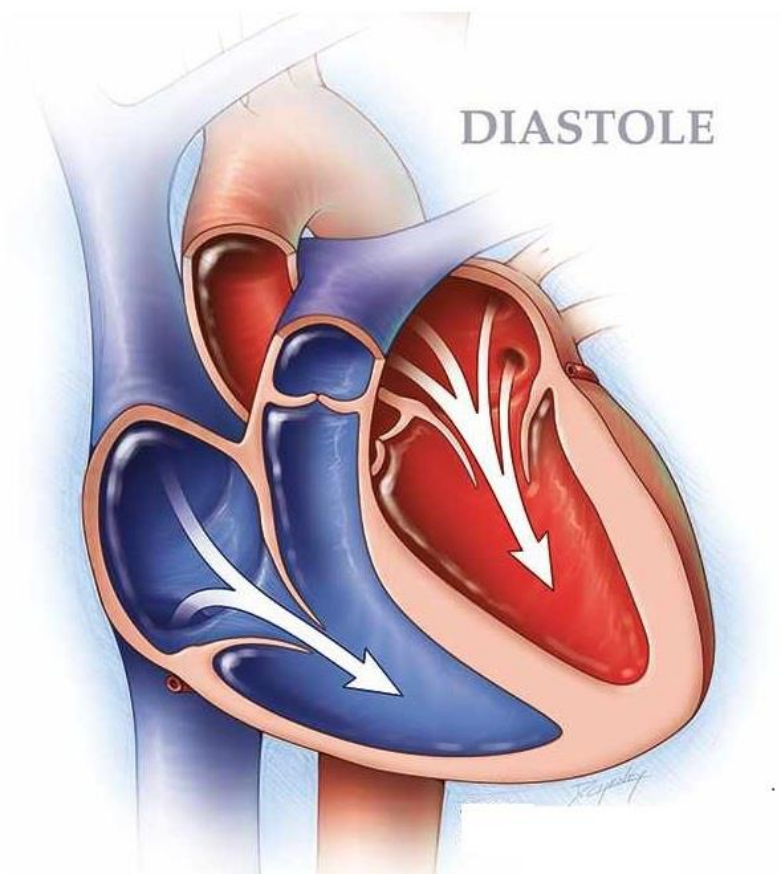


- Lets watch this video

Systole and Diastole

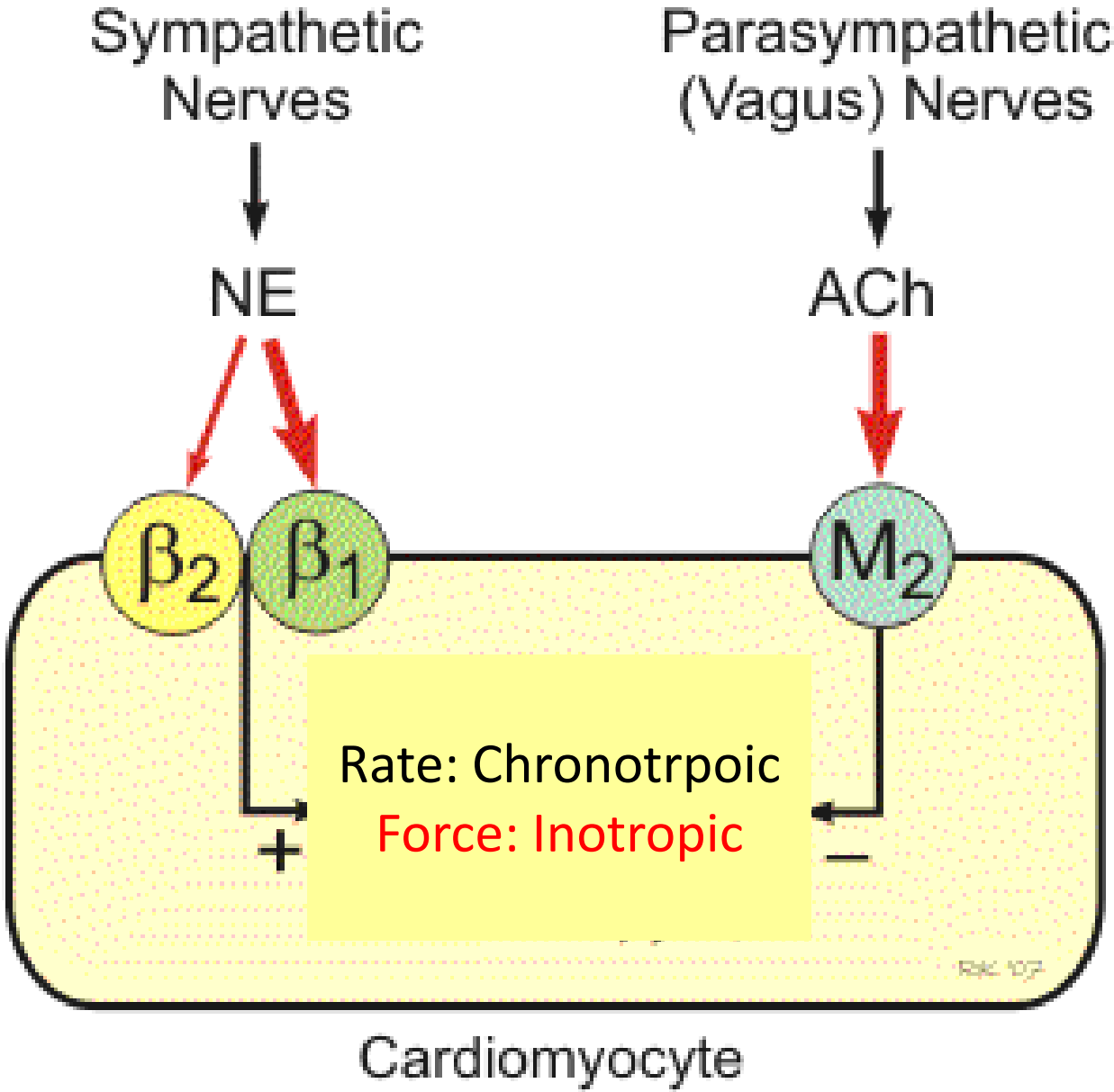


When Ventricle contracts

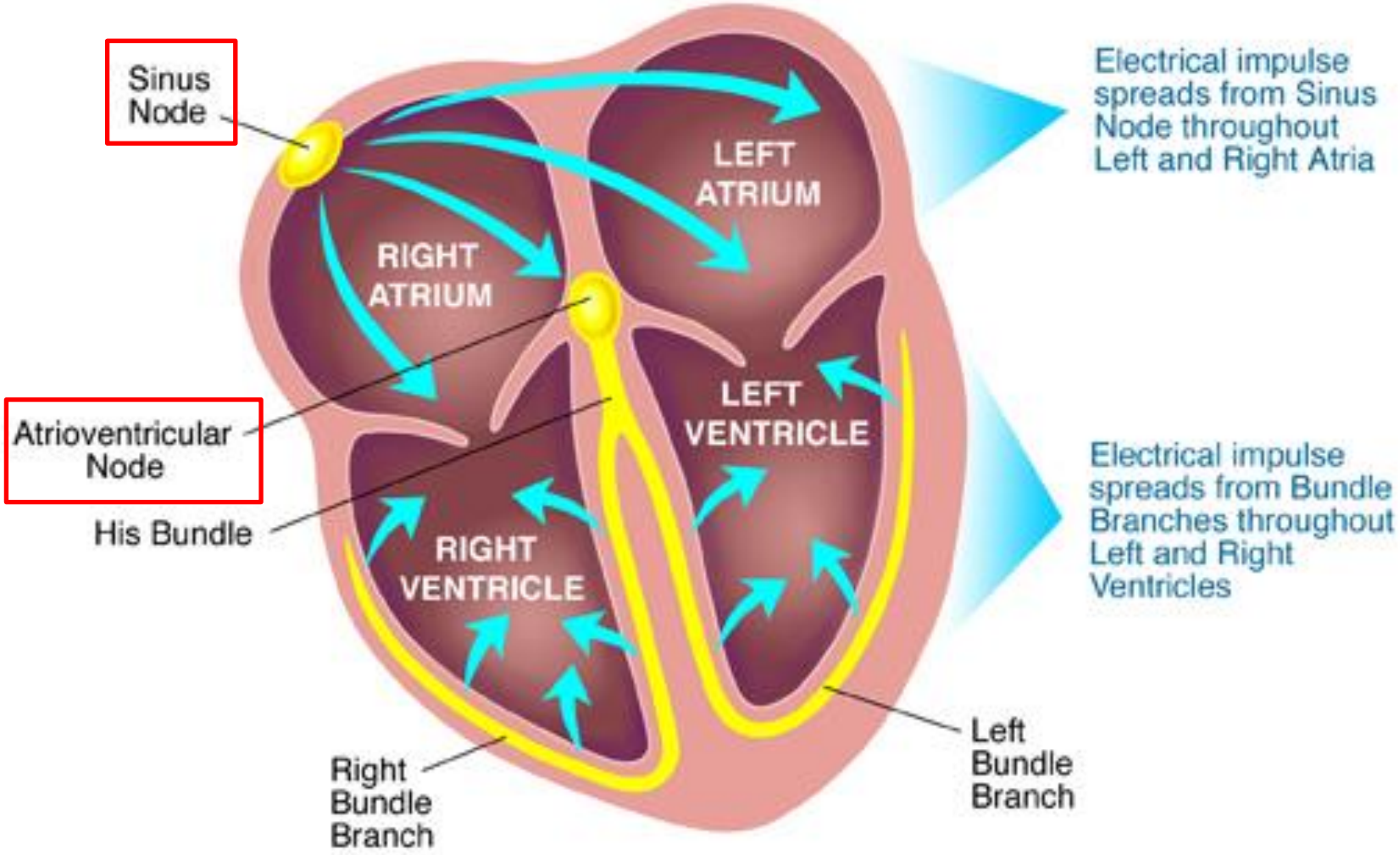


When ventricles relaxes

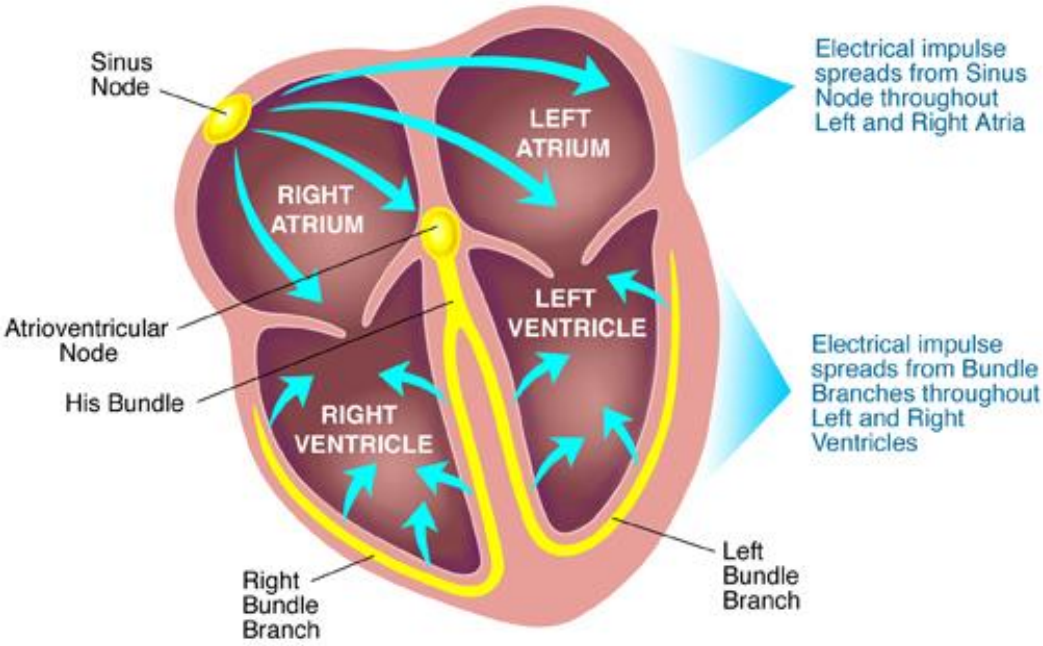
Nerve supply and Receptors on Heart Muscles



How the heart beats?



How the heart beats?



Cardiac Electrical conduction system

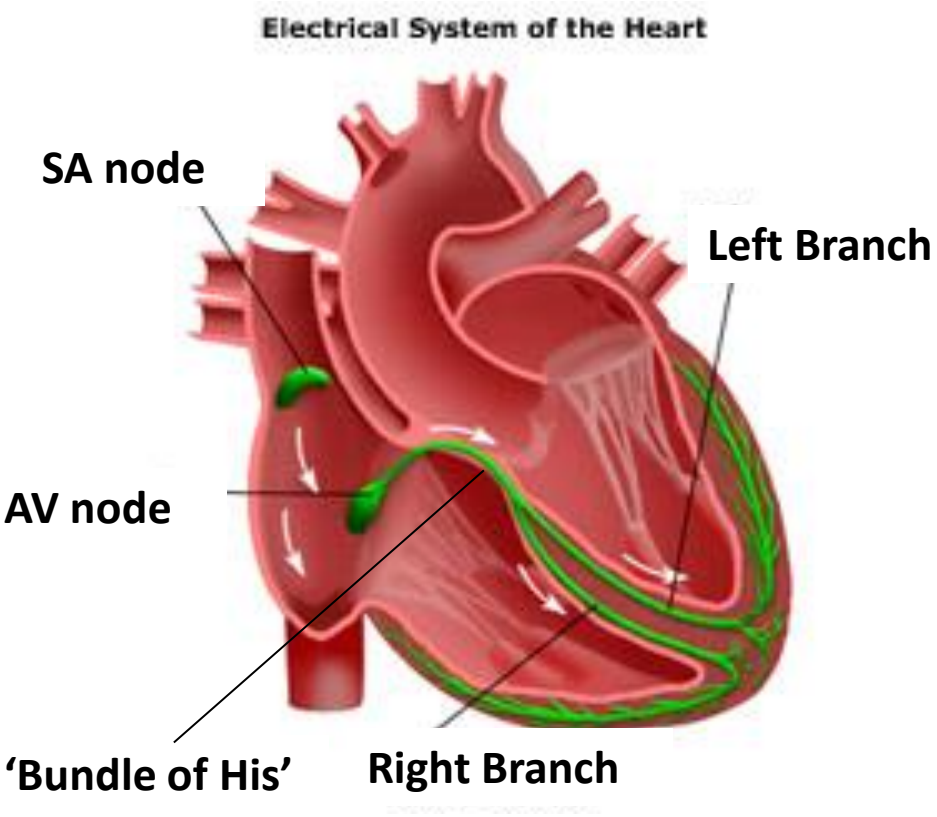
- **Sinoatrial (SA) node:** Pacemaker of heart that initiate electrical impulses and signal get spread to atria via conducting cells
- **Atrioventricular (AV) node:** transmit the electrical impulses to ventricles.

- **Bundle of His**: Sends impulses from AV node to the Purkinje fibers.
  - **Left bundle branch**
  - **Right bundle branch**
- **Purkinje fibers**: make ventricles contract and pump out blood.

- Lets watch another video

Normal Rhythm of the HEART

- 60-100 beats/minute & Originate from SA node



Impulse generates from SA node

↓

Spreads in both Atria

↓

Atria contracts

↓

Impulse moves to AV node

↓

It travels thorough 'Bundle of His'

↓

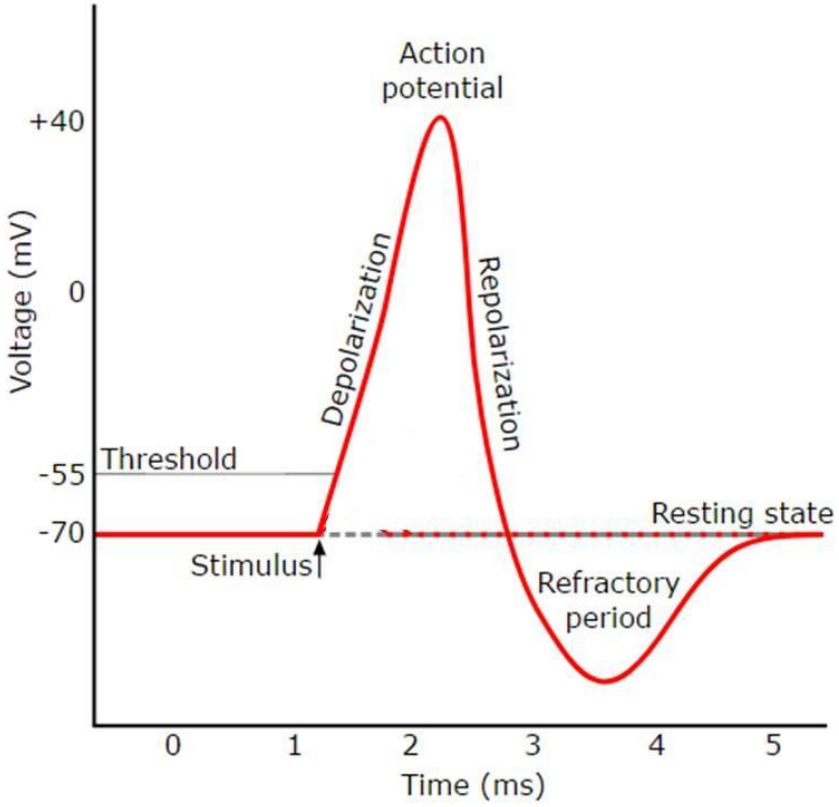
Splits through Right and Left Branches

↓

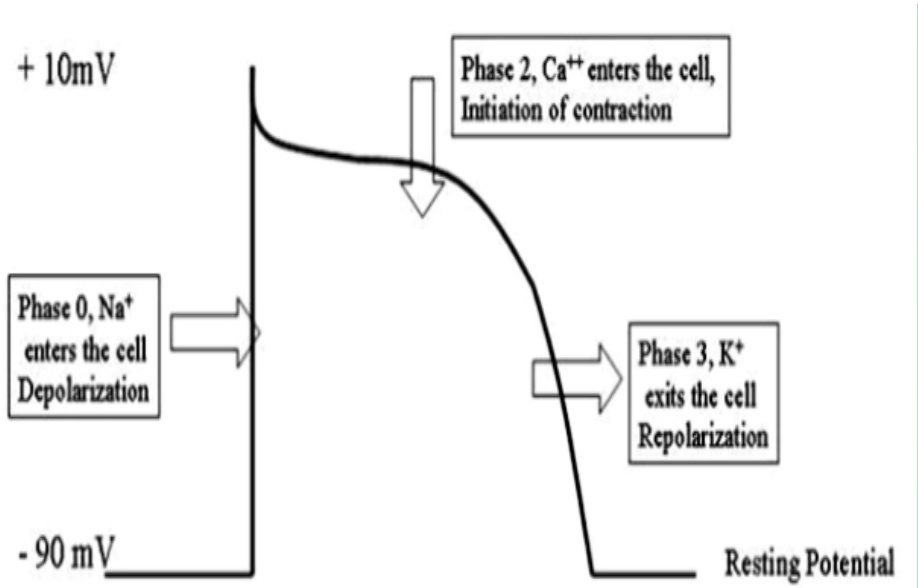
Contraction of both Ventricles

What is action potential?

- A short-term change in the **electrical potential** that travels along a cell, such as a **nerve or muscle fiber or cardiac cell,** and **allows cell to communicate.**
- **The impulse or signal travels in the form of action potential**



Non cardiac cell

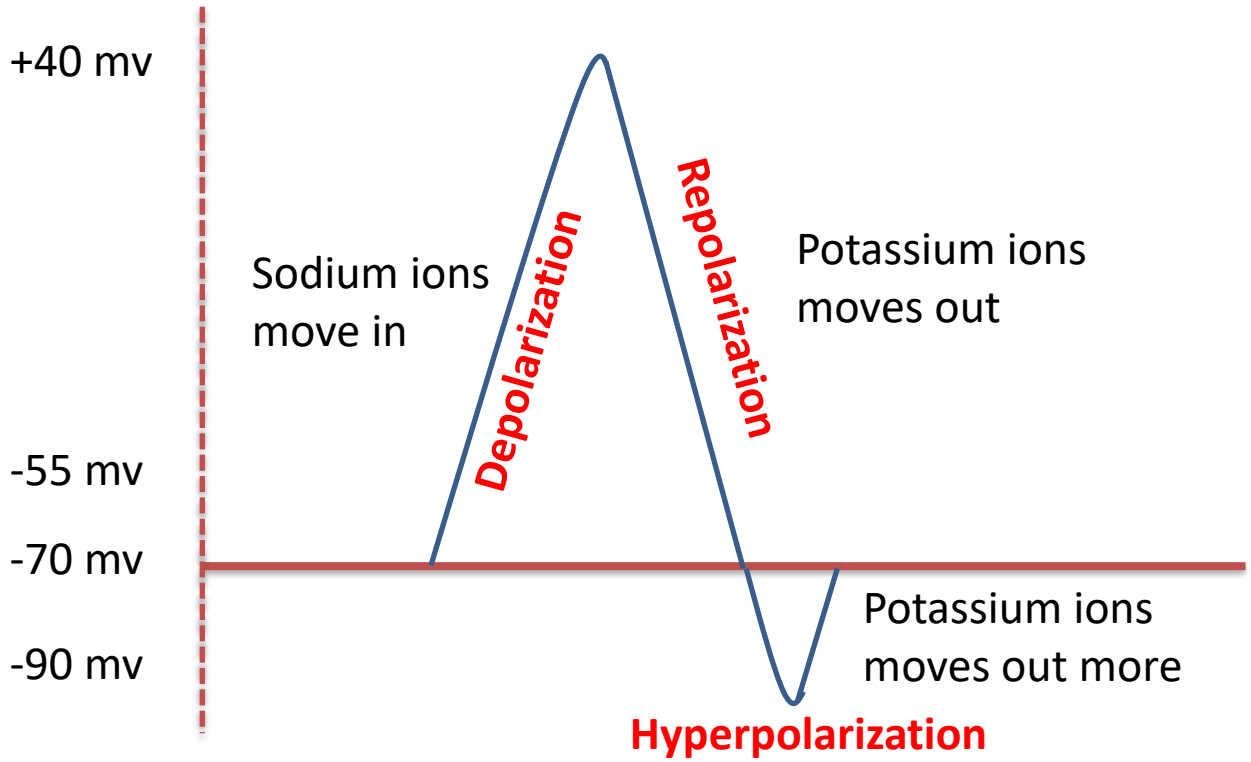


cardiac cell

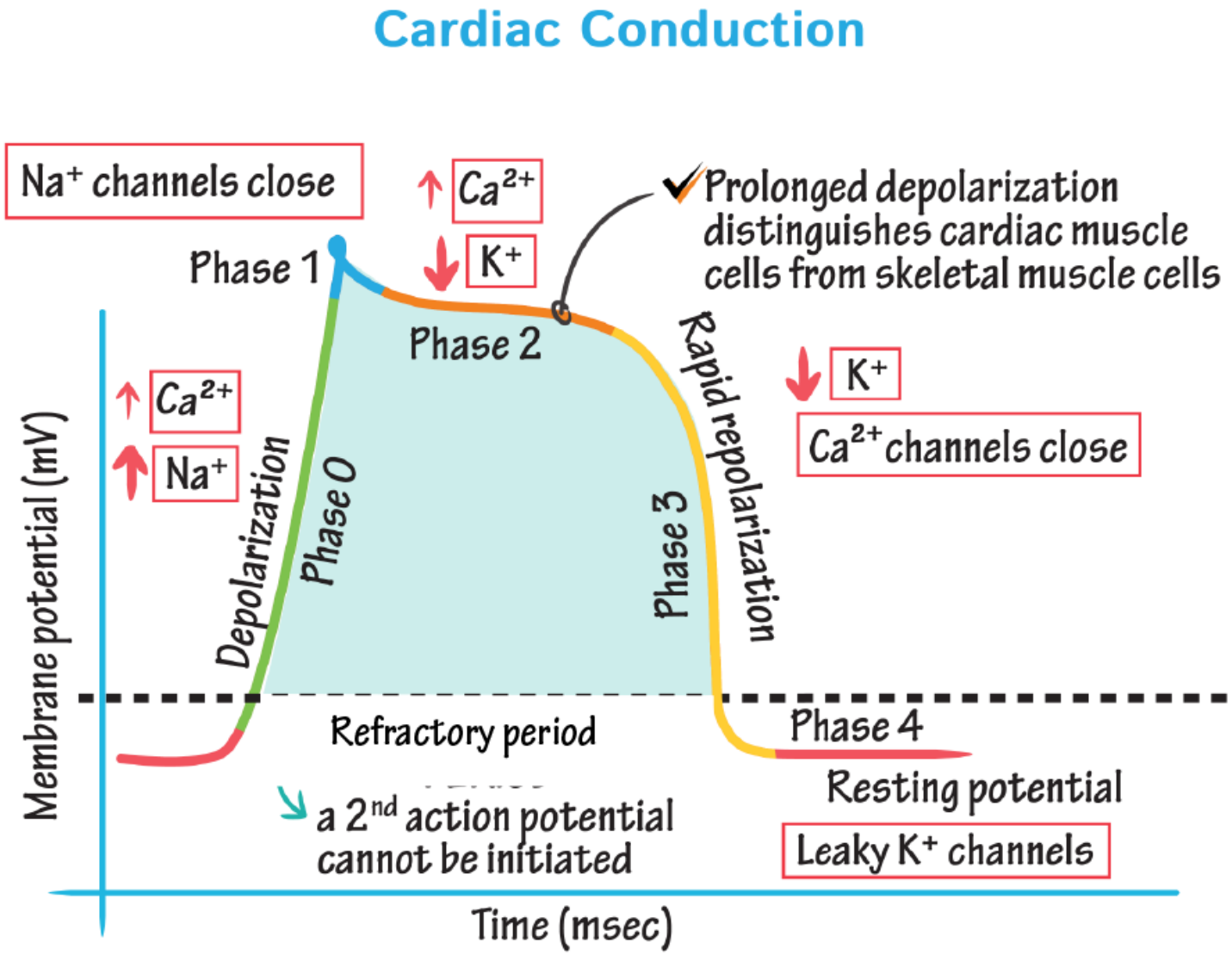
Phases of Action potential

- **Depolarization:** When the (internal) membrane potential becomes positive
- **Repolarization:** When the (internal) membrane potential becomes negative
- **Hyperpolarization:** When the (internal) membrane potential becomes more negative than the resting potential

Phases of Action potential

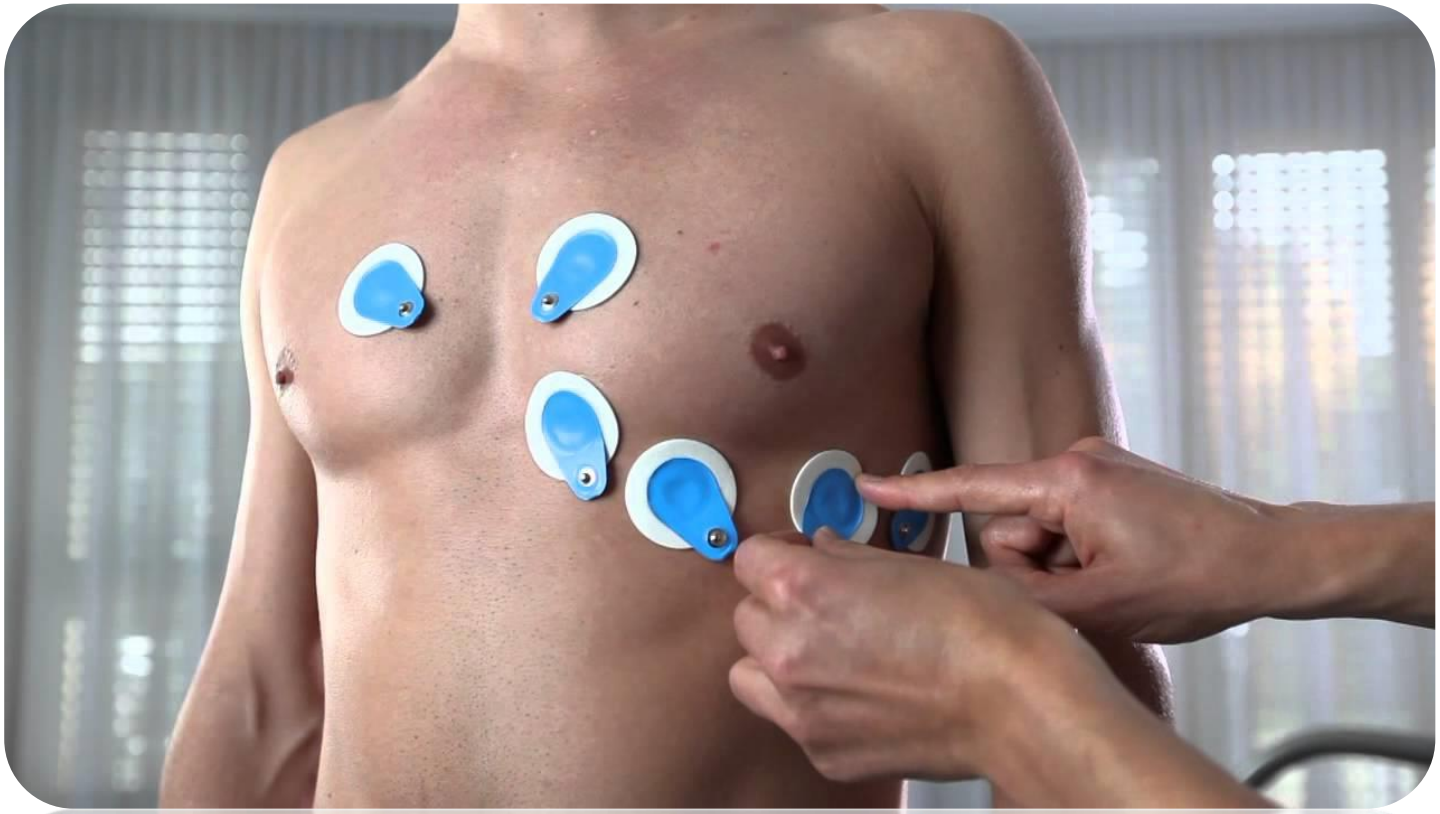


What is action potential?

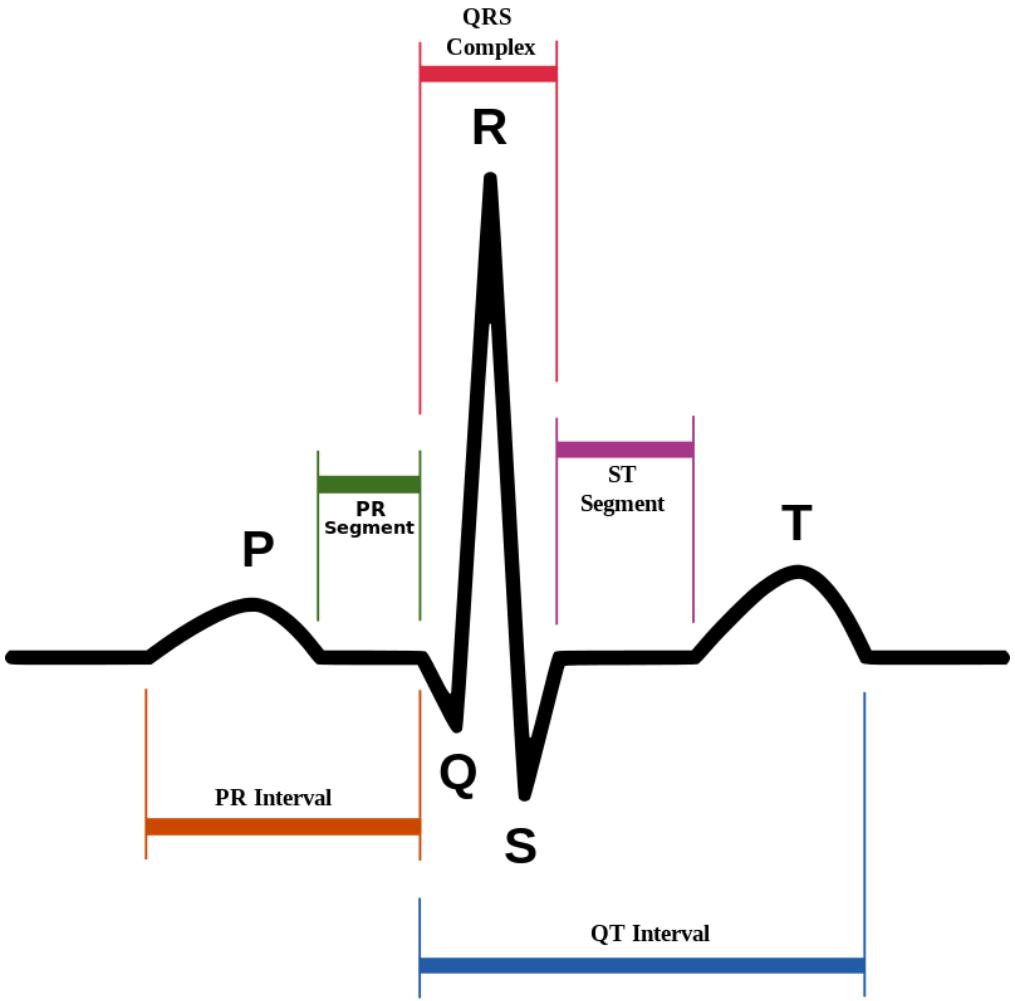


What is ECG?

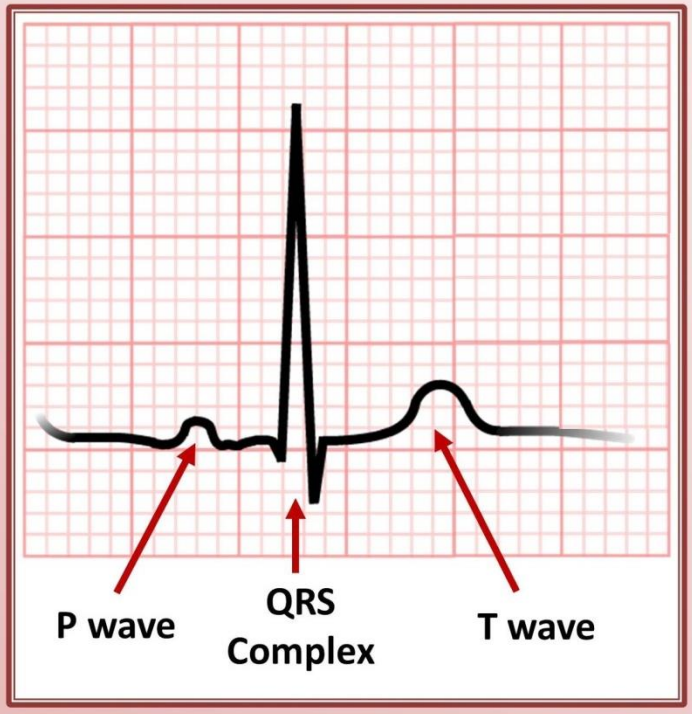
- Process of recording the **electrical activity of the heart** over a period of time using electrodes placed on the skin



Waves in ECG


QRS
Complex
R
PR
Segment
ST
Segment
P
T
Q
S
PR Interval
QT Interval

Waves in relation to Heart activity

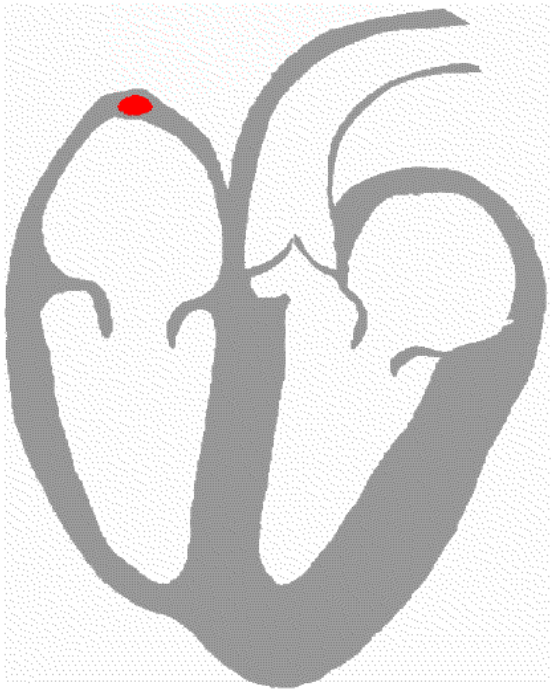


P wave: Atrial Contraction

QRS complex: Ventricular Contraction

T wave: Ventricular Relaxation

Waves in relation to Heart activity



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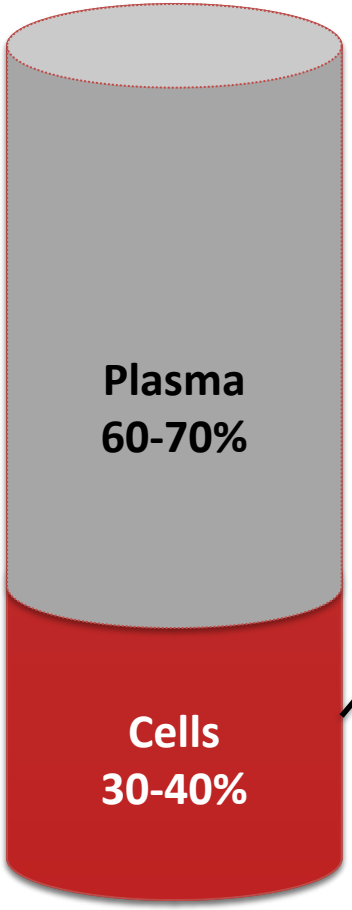
Introduction to Blood

Blood is a liquid connective tissue

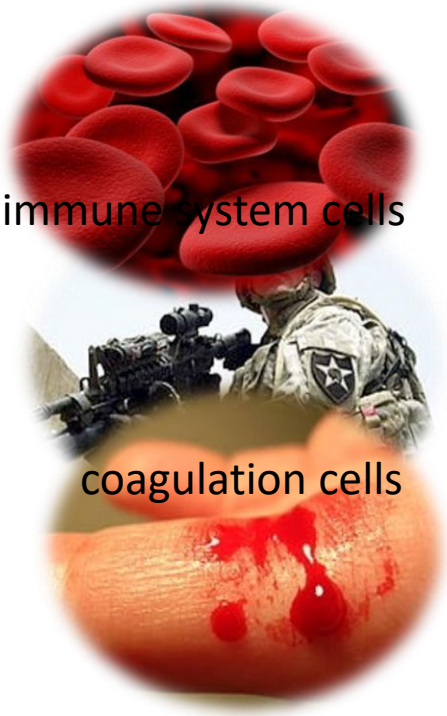


RBC

WBC

Platelets

contain hemoglobin and carry throughout the blood vessels



Functions of Blood

- **Supply of oxygen and nutrients to tissues**
- **Removal of waste products**
- Immunological functions: **Defence mechanism**
- Coagulation: **Formation of blood clot**
- **Regulation** of internal **body temperature**

Thank you

Vasodilatory shock and Vasopressin

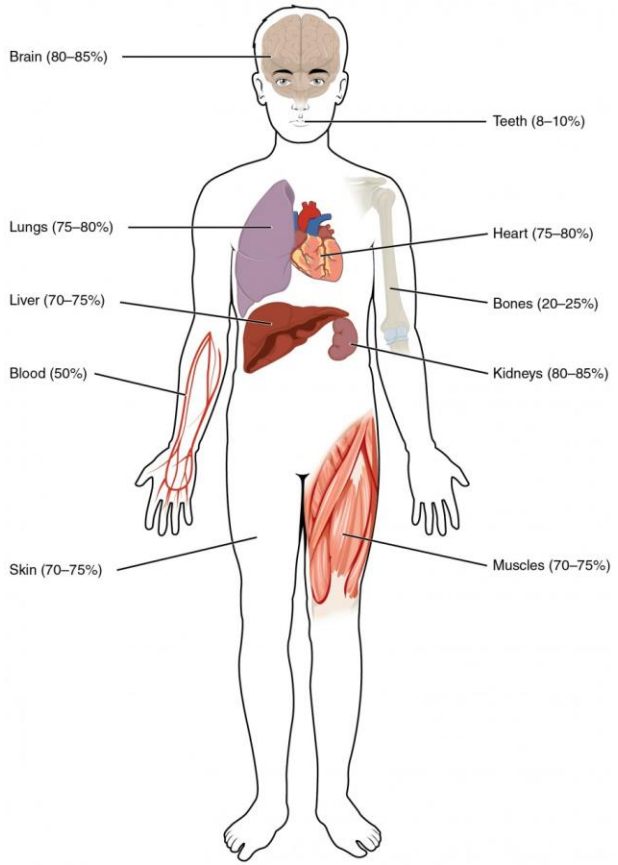
Agenda

- Body fluids and compartments
- Shock
- Shock and common conditions needing lifesaving interventions
- Blood pressure and hypotension
- Bradycardia and AV block
- CPRESSIN
- CPRESSSIN P
- ADRENOR
- ISOLIN

BODY FLUIDS AND COMPARTMENT

Body Fluids and Fluid Compartments

- Human beings are mostly water, ranging from about 75% of body mass in infants to about 50–60 percent in adult men and women, to as low as 45 percent in old age.
- Brain and kidneys have the highest proportions of water, (80–85 percent of their masses).
- Teeth have the lowest proportion of water, (8–10%).

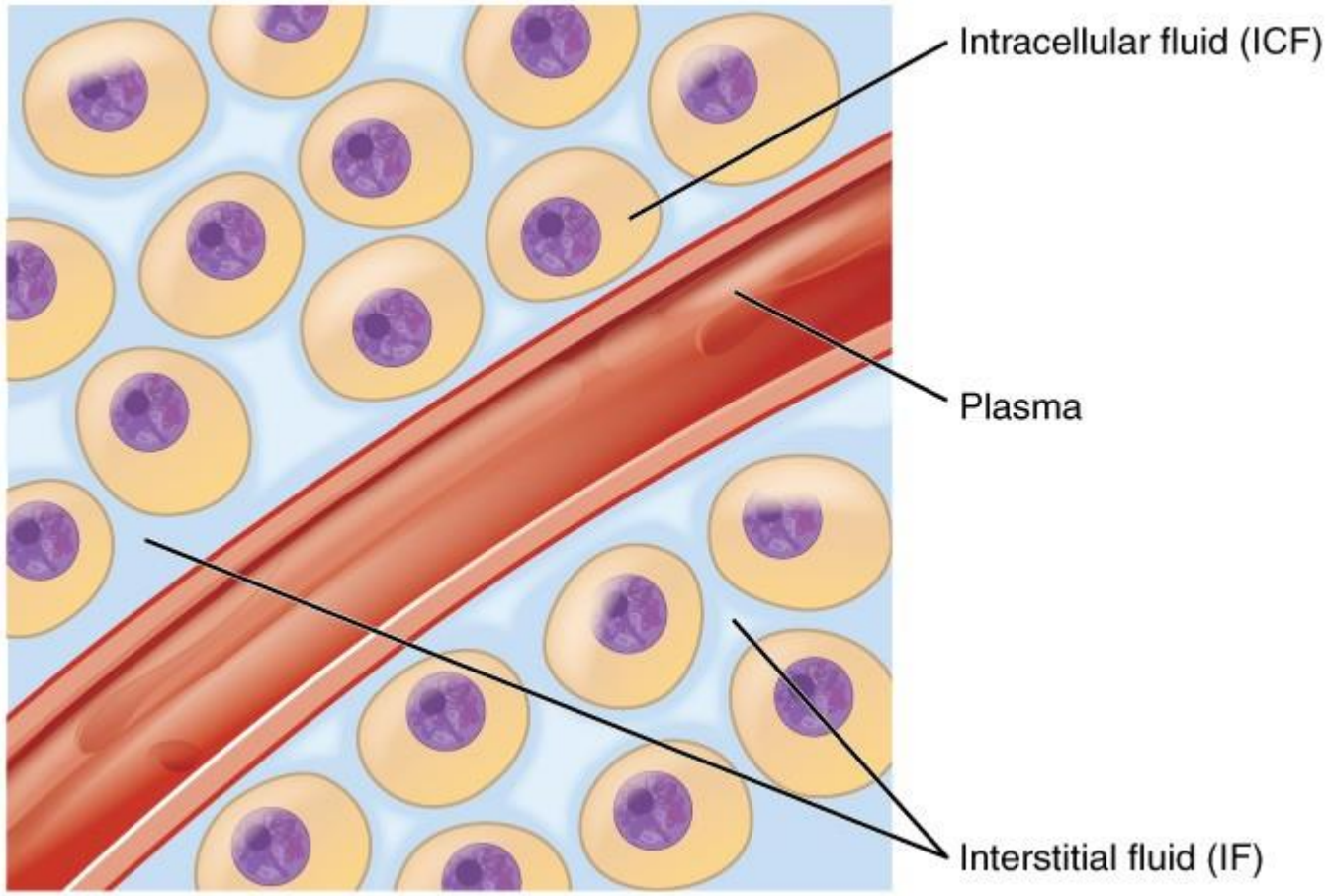


https://courses.lumenlearning.com/suny-ap2/chapter/body-fluids-and-fluid-compartments-no-content/

Fluid Compartments

- Intracellular fluid (ICF)
  - Includes all fluid enclosed in cells by their plasma membranes.
  - 60% of the total water (25 liters)

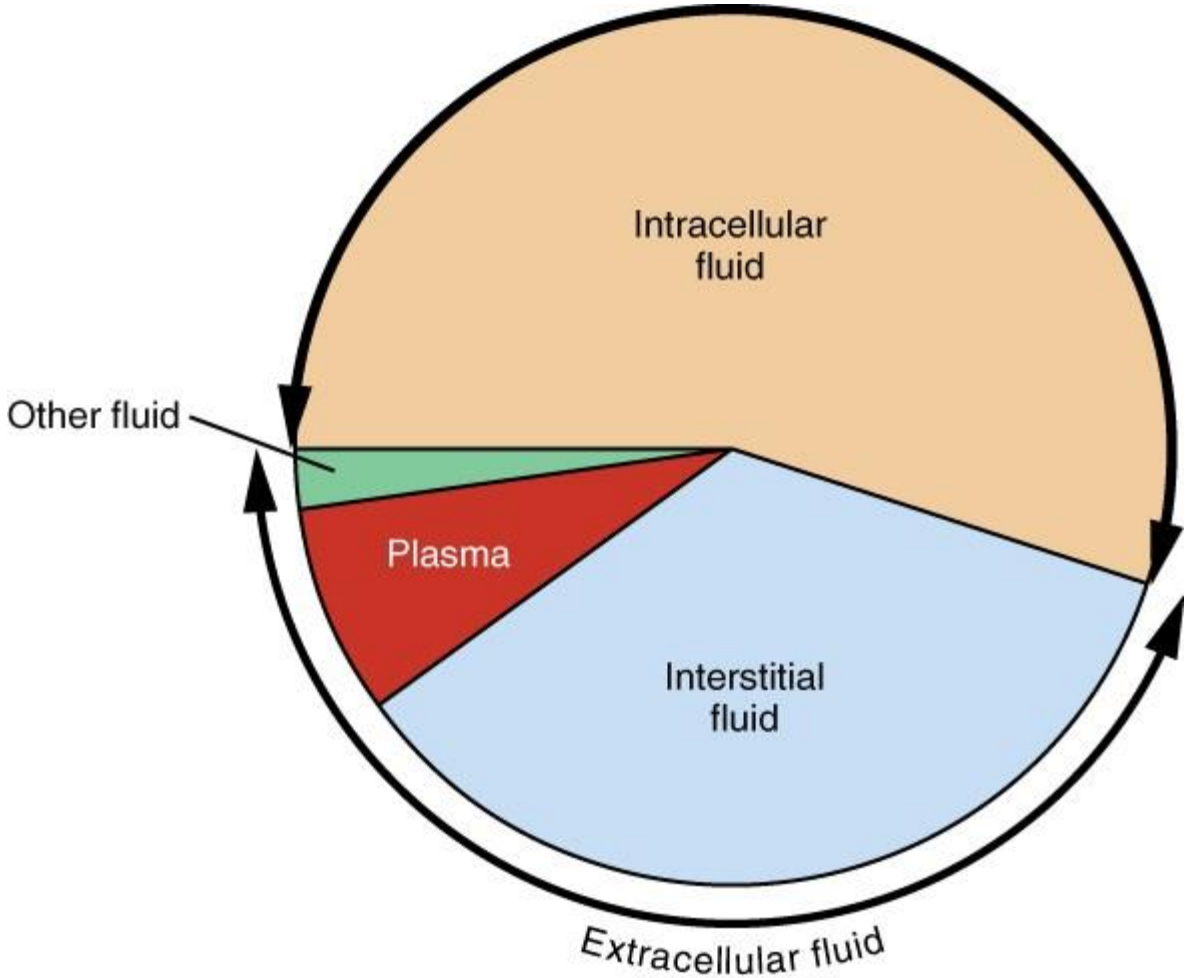
- Extracellular fluid (ECF)
  - Surrounds all cells in the body.
  - Has two primary constituents: the fluid component of the blood (called plasma) and the interstitial fluid (IF) that surrounds all cells not in the blood.
  - 1/3rd of the body's water content
  - 20% of the ECF is found in plasma



https://courses.lumenlearning.com/suny-ap2/chapter/body-fluids-and-fluid-compartments-no-content/

Fluid Compartments (Cont..)

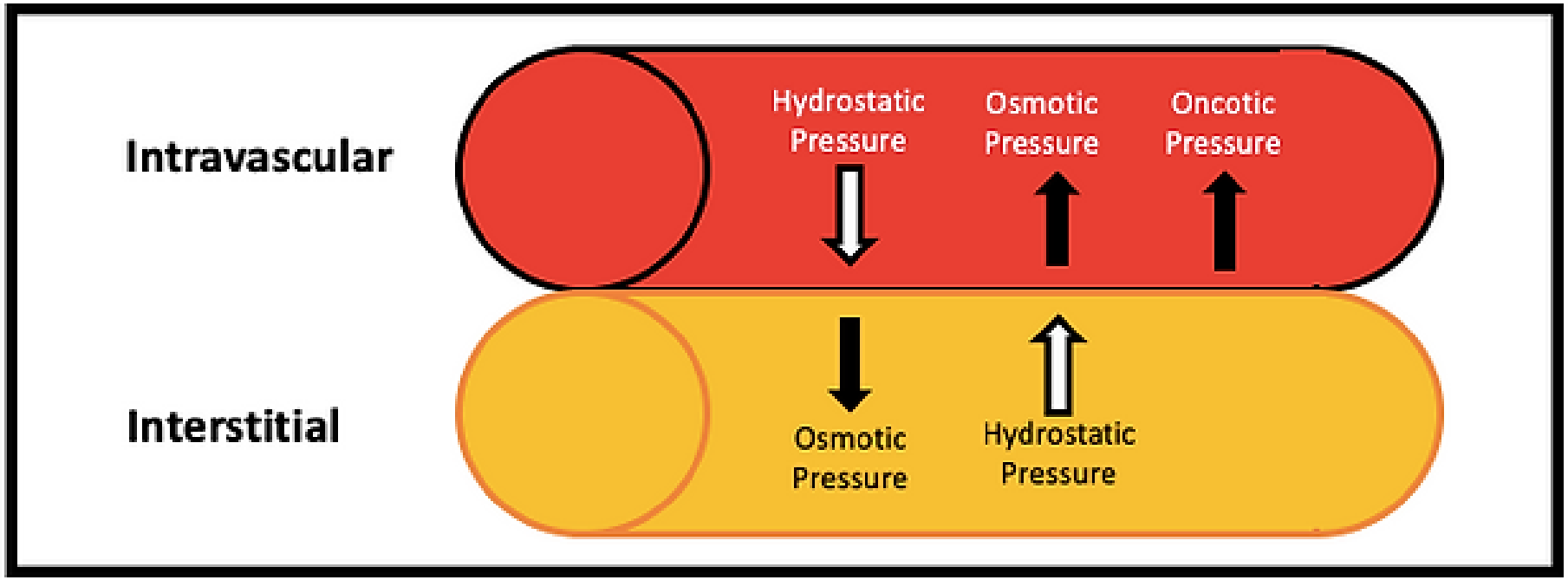
- Most of the water in the body is intracellular fluid.
- The second largest volume is the interstitial fluid, which surrounds cells that are not blood cells.



https://courses.lumenlearning.com/suny-ap2/chapter/body-fluids-and-fluid-compartments-no-content/

keeps fluid in the intravascular space

- Starling forces are the movement of fluid between the intravascular and interstitial space
- Changes in Starling forces lead to complications that can range from hypovolemic shock, volume overload, and pulmonary edema with respiratory failure



https://www.fizzicu.com/post/why-do-we-give-fluids-in-resuscitation-part-1-background-information

Fluid Movement between Compartments

- Osmotic pressure (Pulls the fluid inside)
  - Occurs in the intravascular and interstitial compartments and opposes each other.
  - The osmolarity in the intravascular space wants to pull fluid in, the same is true for the osmolarity in the interstitial space, but it wants to pull fluid into the interstitial space.
- Oncotic pressure (Pulls the fluid inside)
  - The intravascular space has proteins that also help contribute to the osmotic pressure.
  - There are significantly fewer proteins in the interstitial space and can be considered zero.
- Hydrostatic pressure (Pushes the fluid outside)
  - Is the pressure that wants to push fluid out of the space.
  - The intravascular hydrostatic pressure wants to push fluid into the interstitial space and the interstitial hydrostatic pressure wants to push fluid into the intravascular space.
  - The interstitial hydrostatic pressure is low and usually negligible.

https://www.fizzicu.com/post/why-do-we-give-fluids-in-resuscitation-part-1-background-information

SHOCK AND COMMON CONDITIONS NEEDING LIFESAVING INTERVENTIONS

Shock

- Shock is a clinical syndrome characterized by inadequate tissue perfusion that results in end-organ dysfunction.
- Medical emergency
- Patients often have a combination of more than one form of shock (multifactorial shock), four classes of shock are recognized

https://emedicine.medscape.com/article/168689-overview

Classification of shock

Distributive (vasodilation)

- septic shock, systemic inflammatory response syndrome, neurogenic shock, anaphylactic shock, toxic shock, end-stage liver disease, endocrine shock

Cardiogenic (pump failure)

- myocardial infarction, atrial and ventricular arrhythmias, valve or ventricle septal rupture

Hypovolemic (intravascular volume loss)

- hemorrhagic and nonhemorrhagic fluid losses

Obstructive (physical obstruction of blood circulation and inadequate blood oxygenation)

- pulmonary embolism, pulmonary hypertension, tension pneumothorax, constrictive pericarditis, restrictive cardiomyopathy

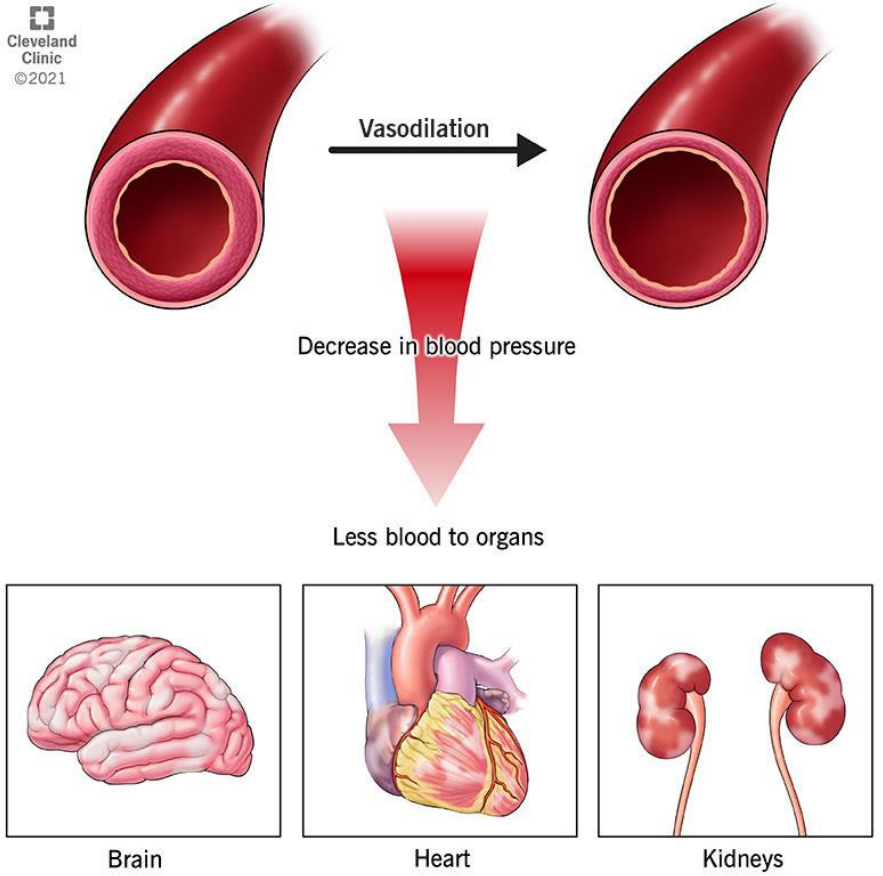
Symptoms

- Depending on the specific cause and type of shock, symptoms will include one or more of the following:
  - Anxiety or agitation/restlessness
  - Bluish lips and fingernails
  - Chest pain
  - Confusion
  - Dizziness, lightheadedness, or faintness
  - Pale, cool, clammy skin
  - Low or no urine output
  - Profuse sweating, moist skin
  - Rapid but weak pulse
  - Shallow breathing
  - Being unconscious (unresponsive)

https://medlineplus.gov/ency/article/000039.htm

Complications of shock

- Organ failure
- Vital organs (heart, brain and kidneys) can’t get enough blood
- This happens because the blood vessels are extremely dilated (flaccid or relaxed), which brings down the blood pressure and cuts down the blood to the organs



https://my.clevelandclinic.org/health/diseases/22762-distributive-shock

Common conditions needing lifesaving interventions

- Anaphylactic shock
- Tension pneumothorax
- Pericardial tamponade
- Hemodynamically significant hemorrhage
- Life-threatening arrhythmias
- Septic shock
- Cardiogenic shock from myocardial infarction
- Cardiogenic shock from acute aortic or mitral valve insufficiency
- Dissection of the ascending aorta
- Hemodynamically significant pulmonary embolism
- Adrenal crisis

Anaphylactic shock

- Anaphylaxis is an acute, potentially fatal, multiorgan system reaction caused by the release of chemical mediators from mast cells and basophils
- Causes
  - Most common inciting agents in anaphylaxis are foods, hymenoptera stings, and intravenous (IV) contrast materials
- Presentation
  - Initially, patients often experience pruritus and flushing

Signs and symptoms

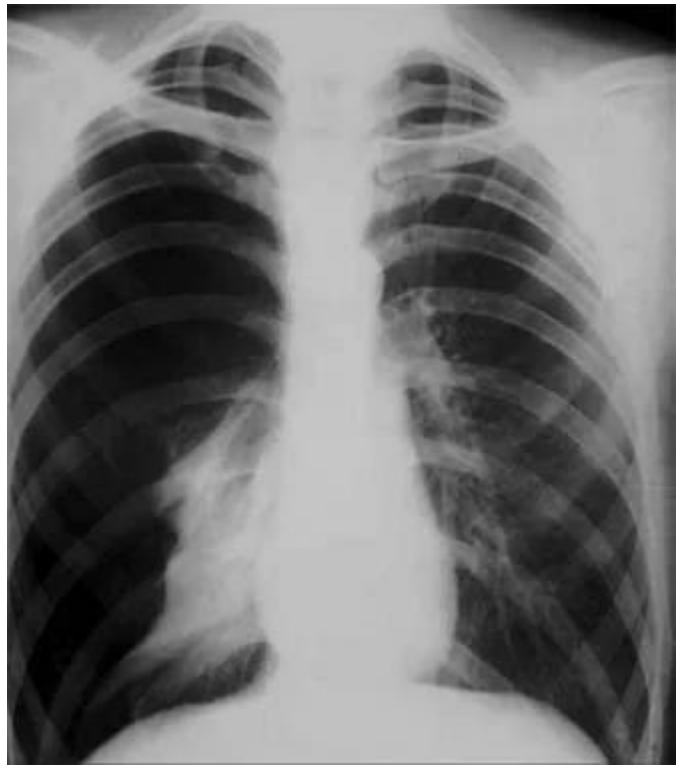
- Classic symptoms of anaphylaxis
  - flushing;
  - urticaria/angioedema;
  - pruritus;
  - bronchospasm;
  - laryngeal edema;
  - abdominal cramping with nausea, vomiting, and diarrhea; and
  - feeling of impending doom

Prevalence of anaphylaxis

- Lifetime prevalence of anaphylaxis is 1-2% of the population as a whole
- Fatal anaphylaxis is infrequent but not rare; milder forms occur much more frequently.
- Up to 500-1000 fatal cases of anaphylaxis per year are estimated to occur in the United States.
- Estimated mortality rates range from 0.65-2% of patients with anaphylaxis

Pneumothorax

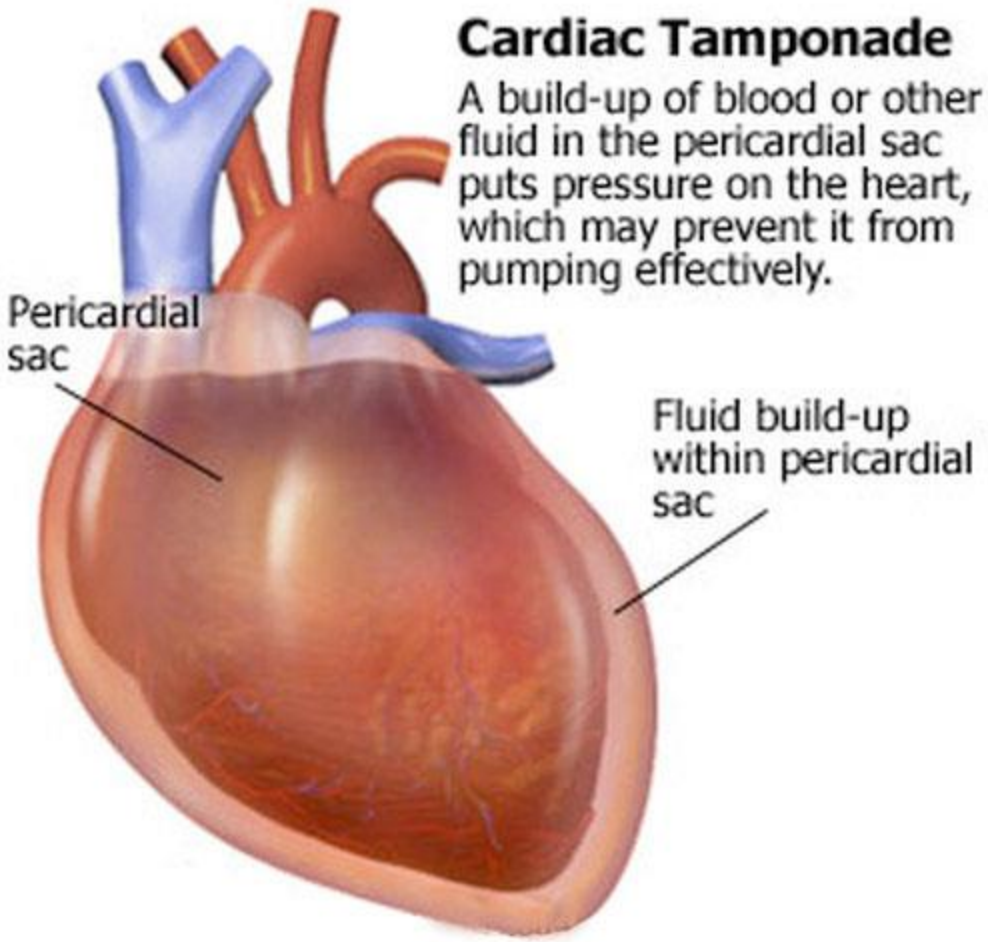
- Pneumothorax is defined as the presence of air or gas in the pleural cavity (ie, the potential space between the visceral and parietal pleura of the lung), which can impair oxygenation and/or ventilation.
- Tension pneumothorax is an emergency.
- Tension pneumothorax presents with hypotension, hypoxia, chest pain, dyspnea
- Tension pneumothorax develops in 1% to 2% of cases initially presenting as idiopathic spontaneous pneumothorax



Radiograph of patient with a complete right-side pneumothorax due to stab wound.

Pericardial tamponade

- Cardiac tamponade is a clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
- The condition is a medical emergency, the complications of which include pulmonary edema, shock, and death



Signs and Symptoms

- Symptoms vary with the acuteness and underlying cause of the tamponade.
- Patients with acute tamponade may present with dyspnea, tachycardia, and tachypnea.
- Cold and clammy extremities from hypoperfusion are also observed in some patients.

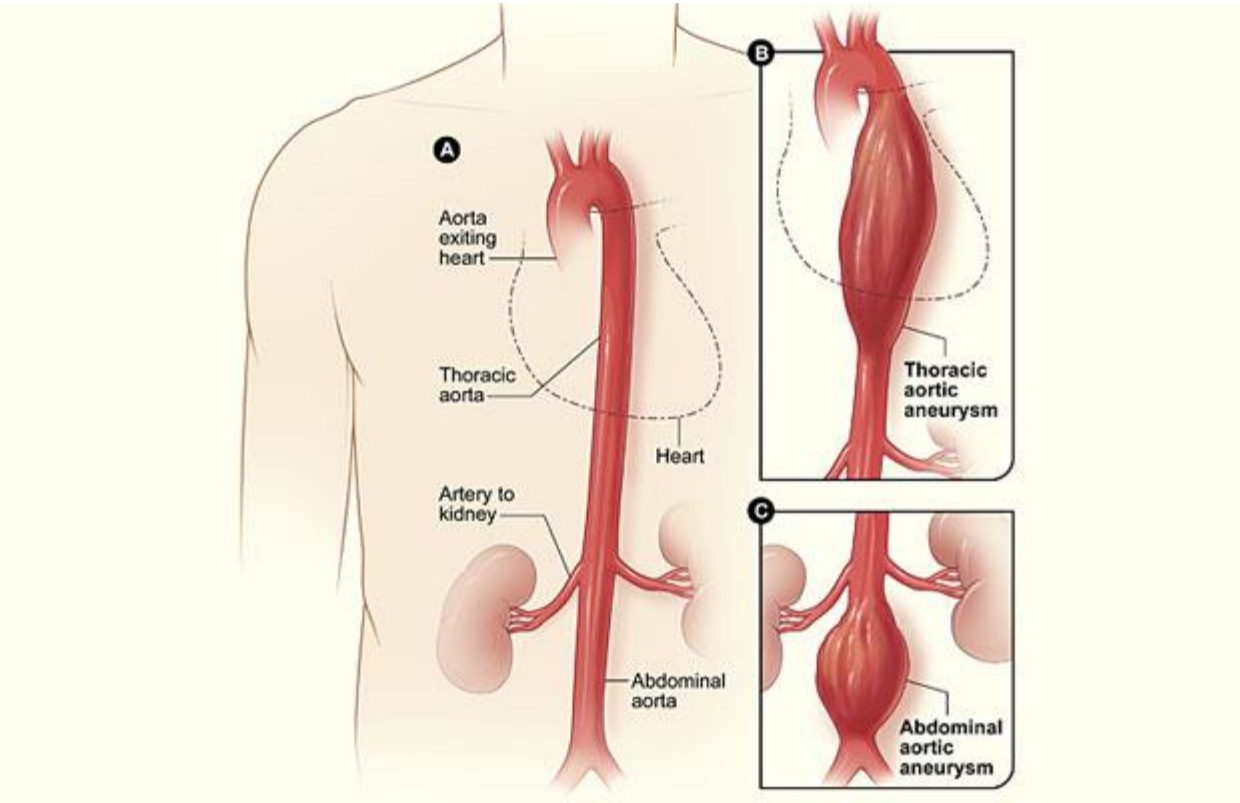
- Other symptoms and signs may include the following:
  - Elevated jugular venous pressure
  - Pulsus paradoxus
  - Chest pressure
  - Decreased urine output
  - Confusion
  - Dysphoria

Etiology and prevalence

- For all patients, malignant diseases are the most common cause of pericardial tamponade
- The incidence of cardiac tamponade is 2 cases per 10,000 population.
- Approximately 2% of penetrating injuries are reported to result in cardiac tamponade.

Hemodynamically significant hemorrhage

- Traumatic – Patients with blunt or penetrating trauma
- Nontraumatic – Patients with ruptured aorta (Aortic aneurysms)
  - Aortic aneurysms are balloon-like bulges that occur in the aorta



Life-threatening arrhythmias

- Ventricular fibrillation (VF) is a life-threatening cardiac arrhythmia in which the coordinated contraction of the ventricular myocardium is replaced by high-frequency, disorganized excitation, resulting in [the effective] failure of the heart to pump blood.
- VF is the most commonly identified arrhythmia in cardiac arrest patients.
- In the prehospital setting, 65%-85% of patients in cardiac arrest have VF identified as the initial rhythm by emergency services personnel
- VF usually ends in death within minutes unless prompt corrective measures are instituted.

Etiology and prevalence

- Coronary artery disease (CAD) is the single most common etiologic factor predisposing patients to ventricular fibrillation (VF).
- Of the approximately 300,000 cases of sudden cardiac death (SCD) that occur each year, up to one third are attributed to VF.

Septic shock

- Septic shock is the last and most severe stage of sepsis.
- Sepsis occurs when the immune system has an extreme reaction to an infection.
- The inflammation throughout the body can cause dangerously low blood pressure.

Signs and symptoms

- Symptoms are often nonspecific
- Fever (usually >101°F [38°C]), chills, or rigors
- Confusion
- Anxiety
- Difficulty breathing
- Fatigue, malaise
- Nausea and vomiting
- In sepsis, symptoms may include decreased urine output and cyanosis (blueish discoloration of the lips and/or digits).

Etiology and prevalence

- Etiology
  - The most common disease states predisposing to sepsis are malignancies, diabetes mellitus, chronic liver disease, and chronic kidney disease.
  - The use of immunosuppressive agents is also a common predisposing factor.
  - In addition, sepsis is a common complication after major surgery, trauma, and extensive burns.
  - Patients with indwelling catheters or devices are also at high risk

- Prevalence
  - An analysis of a large sample from major US medical centers reported the incidence of sepsis (at the time, deemed severe sepsis) as 3 cases per 1000 population and 2.26 cases per 100 hospital discharge

Cardiogenic shock from myocardial infarction

- Cardiogenic shock is defined as a decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume
- Cardiogenic shock is the leading cause of death in acute myocardial infarction (MI), with mortality rates as high as 70-90%
- The incidence rate of cardiogenic shock ranges from 5% to 10% in patients with acute MI.

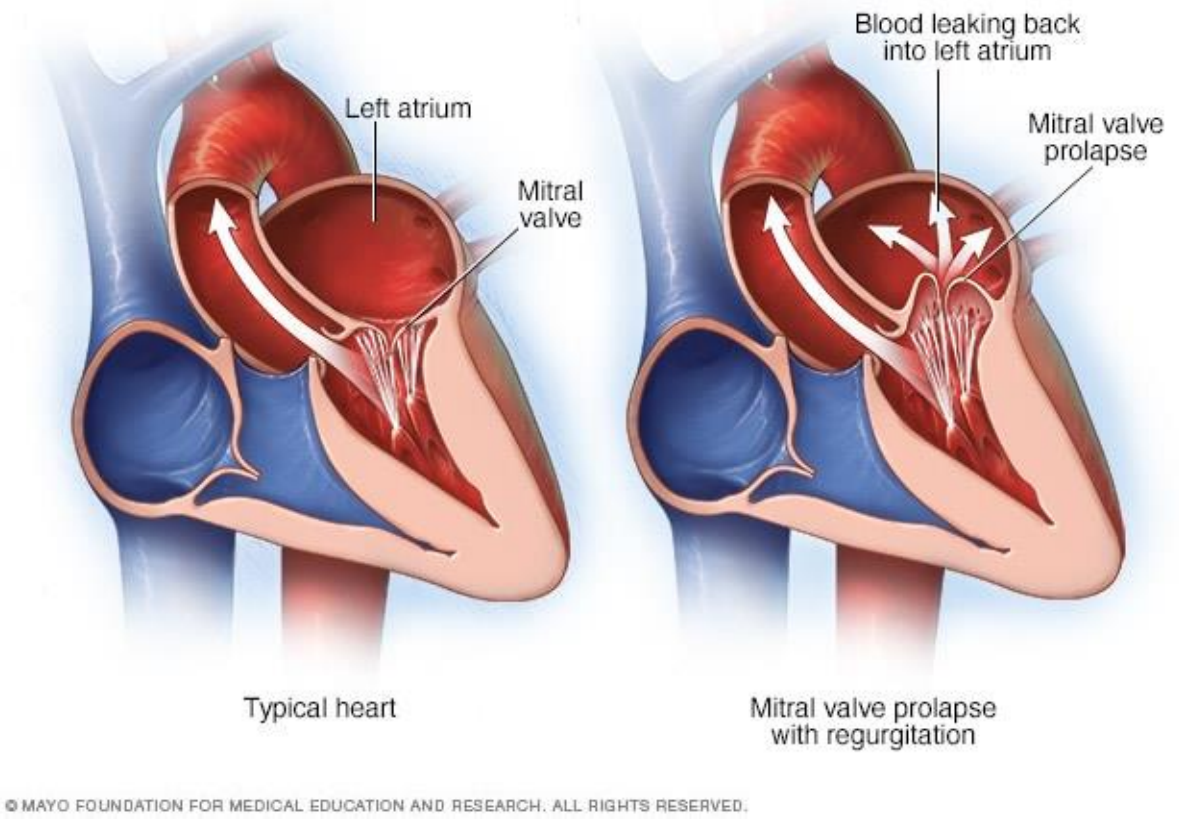
Signs and symptoms

- Hypotension
- Absence of hypovolemia
- Clinical signs of poor tissue perfusion (ie, oliguria, cyanosis, cool extremities, altered mentation)

Cardiogenic shock from acute aortic or mitral valve insufficiency

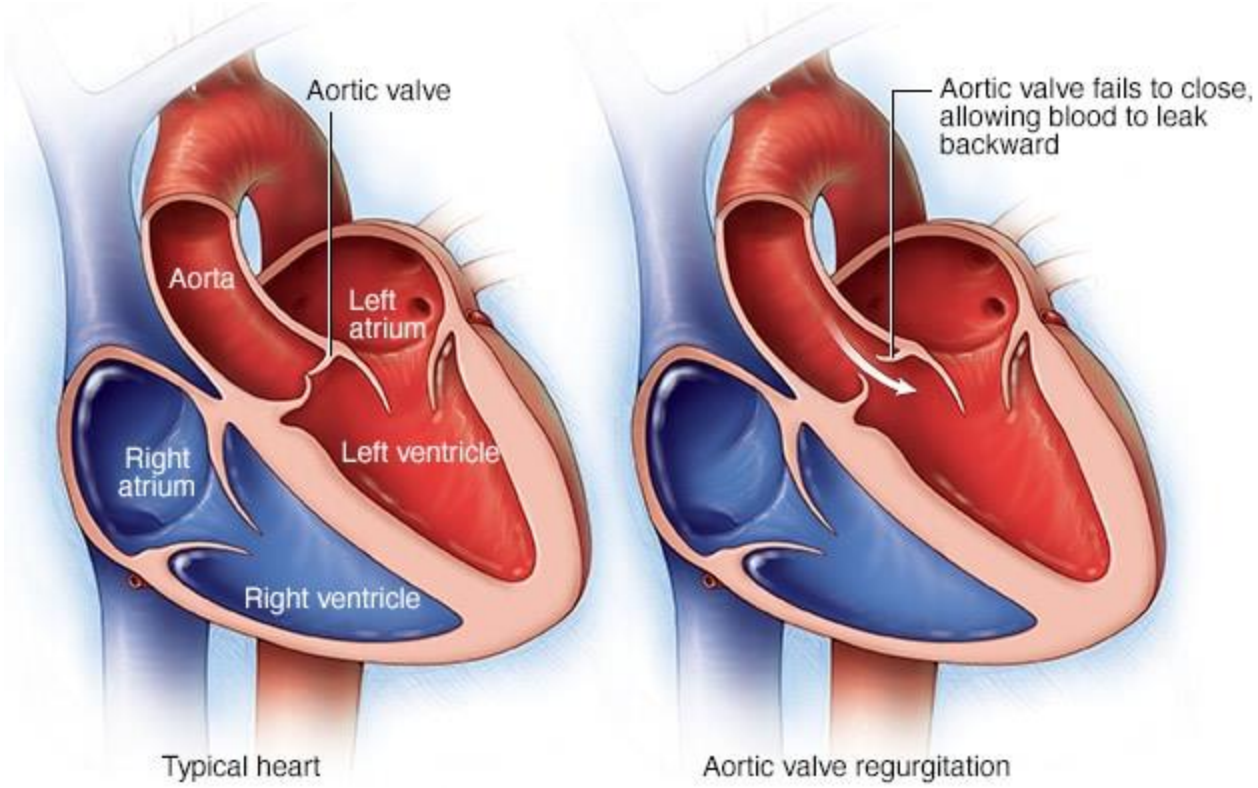
- Mitral regurgitation (MR) is defined as an abnormal reversal of blood flow from the left ventricle (LV) to the left atrium (LA). It is caused by disruption in any part of the mitral valve (MV) apparatus.

- Most common etiologies
  - MV prolapse (MVP),
  - rheumatic heart disease,
  - infective endocarditis,
  - annular calcification,
  - cardiomyopathy, and
  - ischemic heart disease



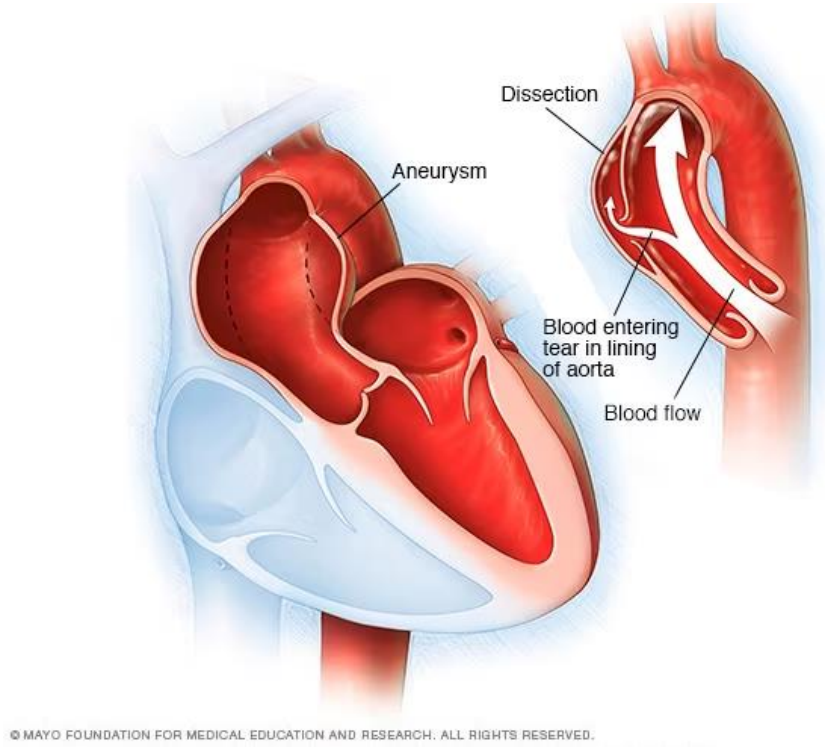
Cardiogenic shock from acute aortic or mitral valve insufficiency (Cont..)

- Aortic regurgitation (AR) is the diastolic flow of blood from the aorta into the left ventricle (LV). Regurgitation is due to incompetence of the aortic valve or any disturbance of the valvular apparatus (eg, leaflets, annulus of the aorta) resulting in the diastolic flow of blood into the left ventricular chamber



Dissection of the ascending aorta

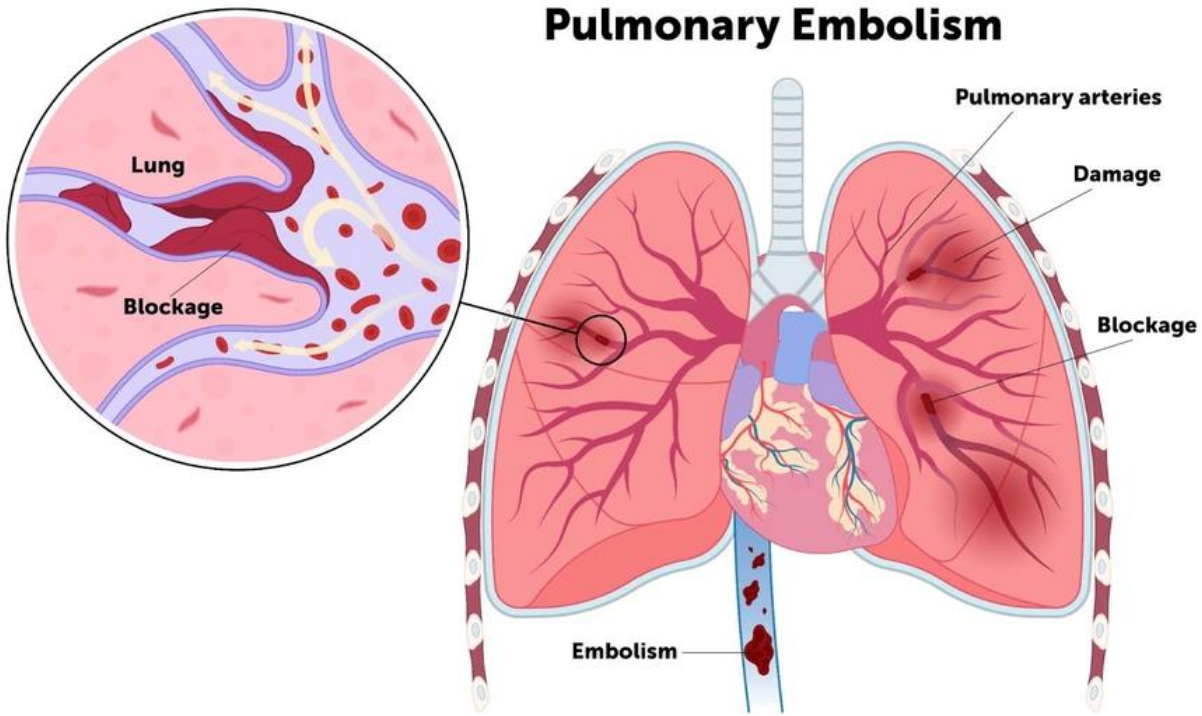
- An aortic dissection is a serious condition in which a tear occurs in the inner layer of the aorta
- Blood rushes through the tear, causing the inner and middle layers of the aorta to split (dissect).
- If the blood goes through the outside aortic wall, aortic dissection is often deadly
- Aortic dissection is relatively uncommon.
- It usually occurs in men in their 60s and 70s.



Hemodynamically significant pulmonary embolism

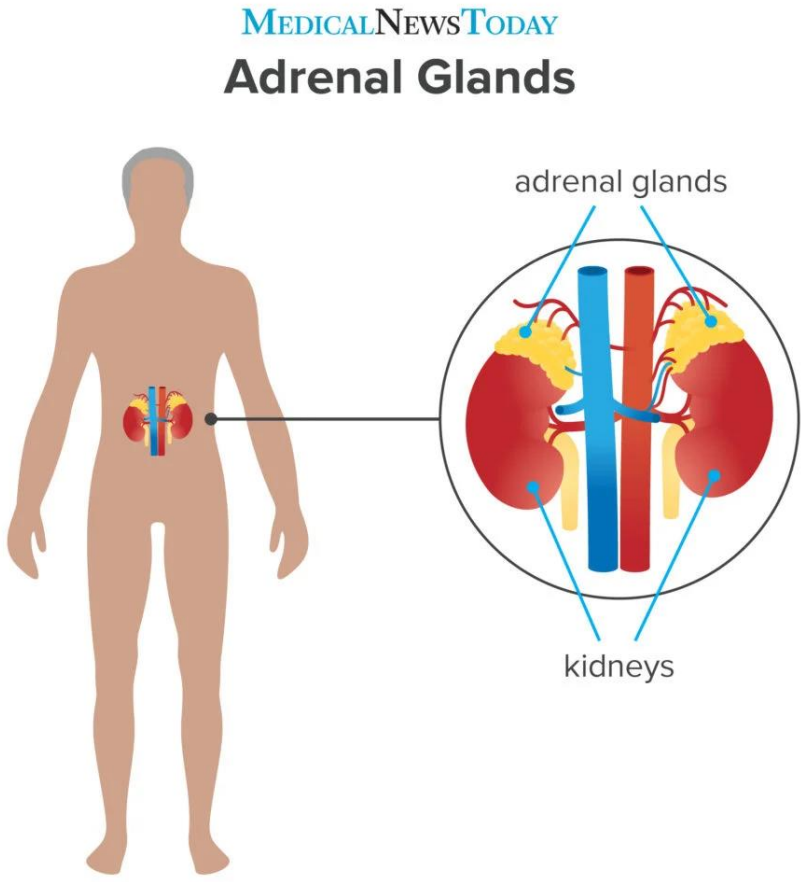
- Pulmonary embolism (PE) occurs when a thrombus originates elsewhere and disrupts blood flow in the pulmonary artery or its branches

- Hemodynamically unstable PE is PE that results in hypotension (as defined by systolic blood pressure (SBP) less than 90 mm Hg or a drop in SBP of 40 mm Hg or more from baseline or hypotension that requires vasopressors or inotropes)



Adrenal crisis

- Adrenal insufficiency
  - is an uncommon illness that occurs when the body doesn't make enough of certain hormones (Cortisol)
- Addisonian crisis
  - Life-threatening situation that results in low blood pressure, low blood levels of sugar and high blood levels of potassium.
  - It requires immediate medical care



Symptoms of adrenal insufficiency

- Extreme fatigue
- Weight loss and loss of appetite
- Areas of darkened skin
- Low blood pressure, even fainting
- Salt craving
- Low blood sugar, also called hypoglycemia
- Nausea, diarrhea or vomiting
- Abdominal pain

Presentation

Hypotension is a common presentation in most of the etiologies of hypovolemic shock

Hypotension means low blood pressure

$$BP < \frac{90}{60}$$

Initial approach in management of shock

- A=Airway
- B=Breathing
- C=Circulation (Fluids, vasopressors)

- The first priorities are to stabilize the airway and breathing with oxygen and/or mechanical ventilation, when necessary.
- Intravenous access should be secured so that patients can be immediately treated with intravenous fluids (IVFs) to restore adequate tissue perfusion

BLOOD PRESSURE AND HYPOTENSION

Blood pressure

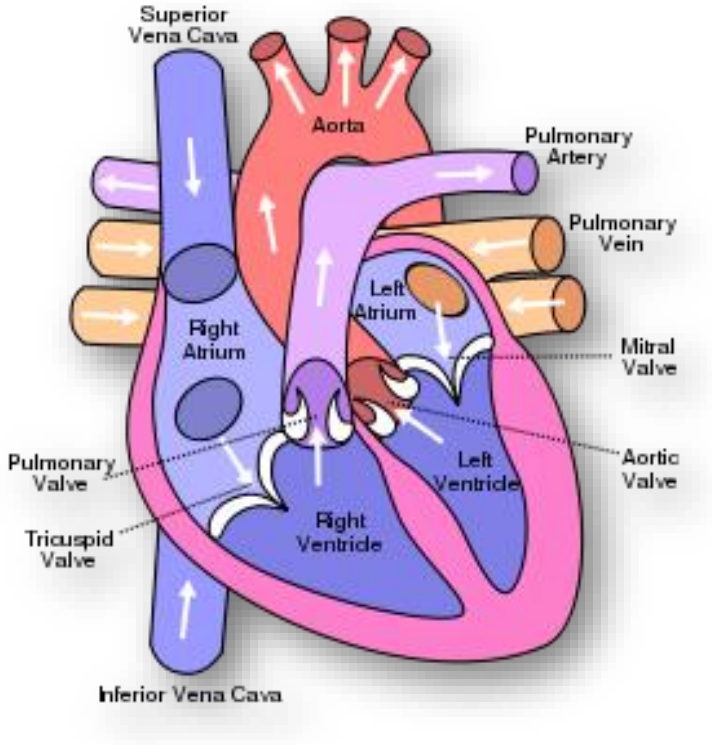
- Lateral pressure exerted by blood against walls of blood vessels, especially arteries

Systolic blood pressure

- Pressure exerted on arterial walls by blood when
- heart is in systole (ventricular contraction)

Diastolic blood pressure

- Pressure exerted on arterial walls by blood when
- heart is in diastole (ventricular relaxation)



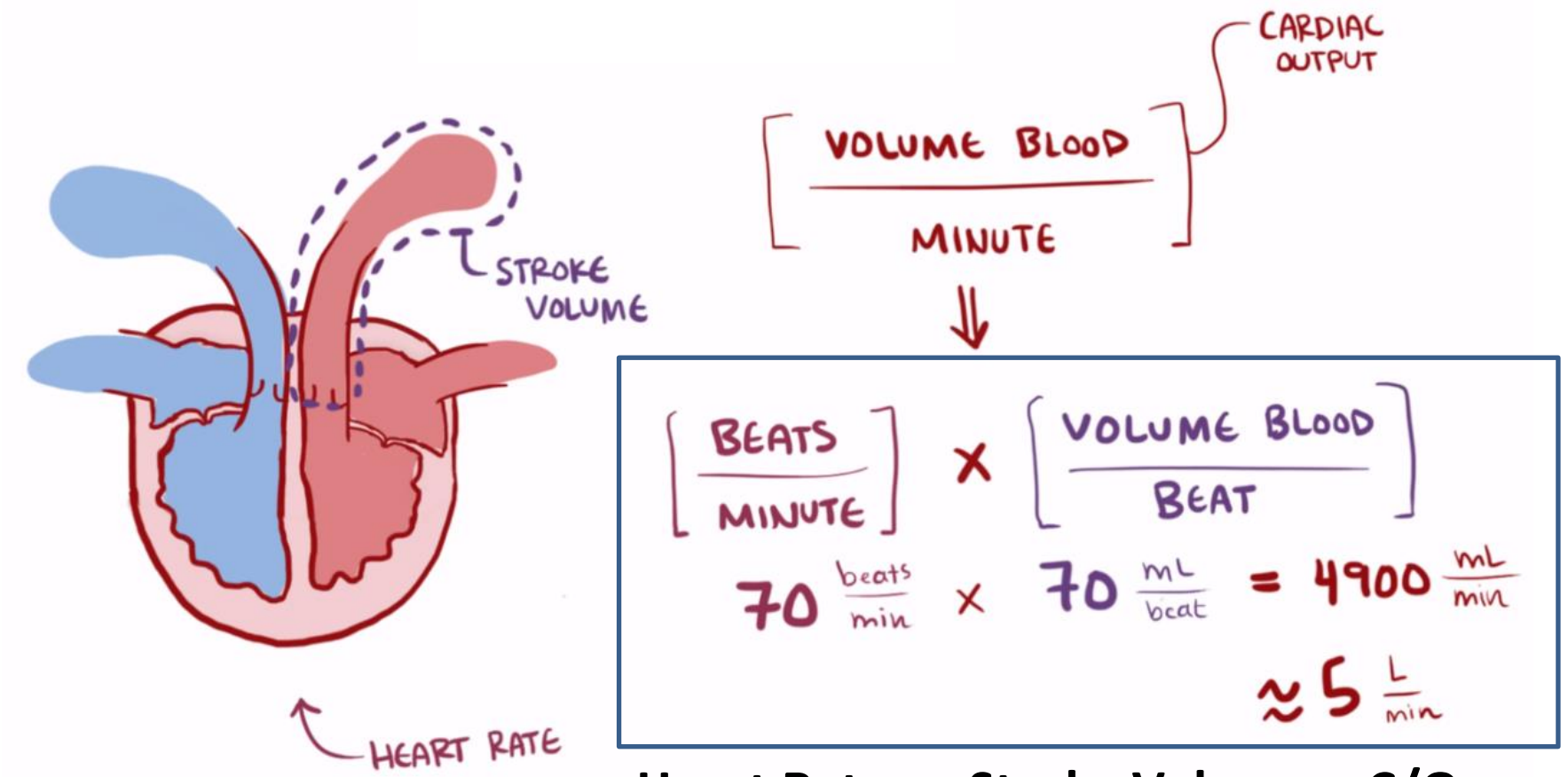
Cardiac output

- Amount of blood that is pumped by heart per minute

Peripheral resistance

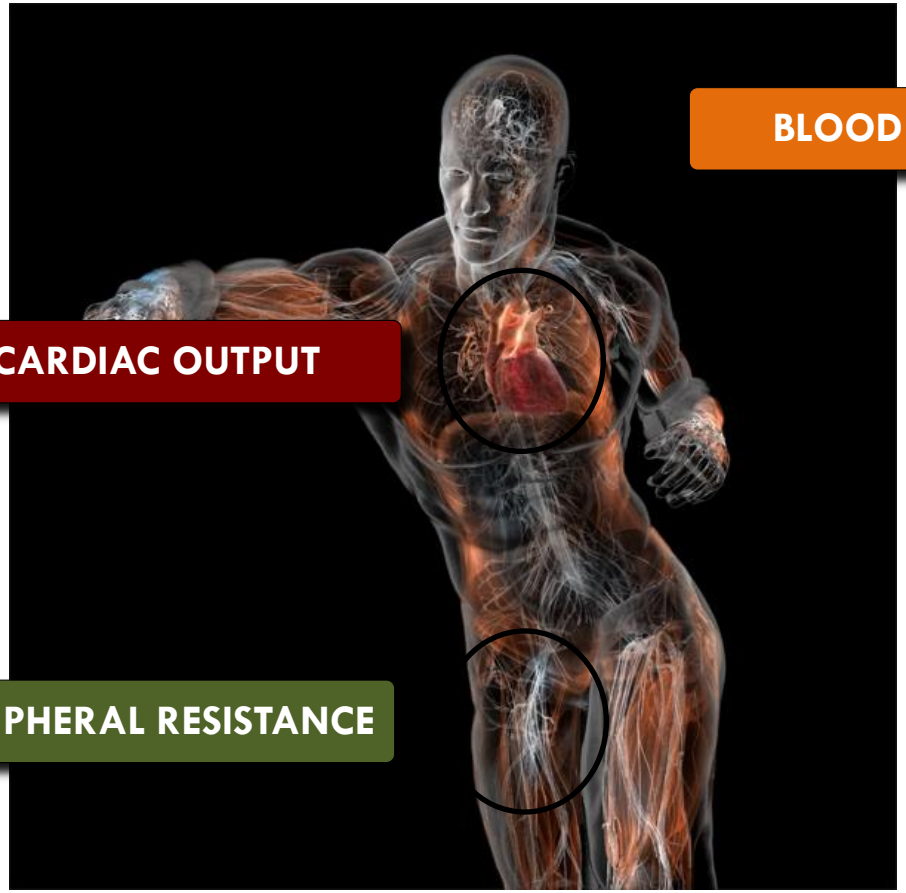
- Sum of resistance of all peripheral vasculature in systemic circulation

Formula of cardiac output



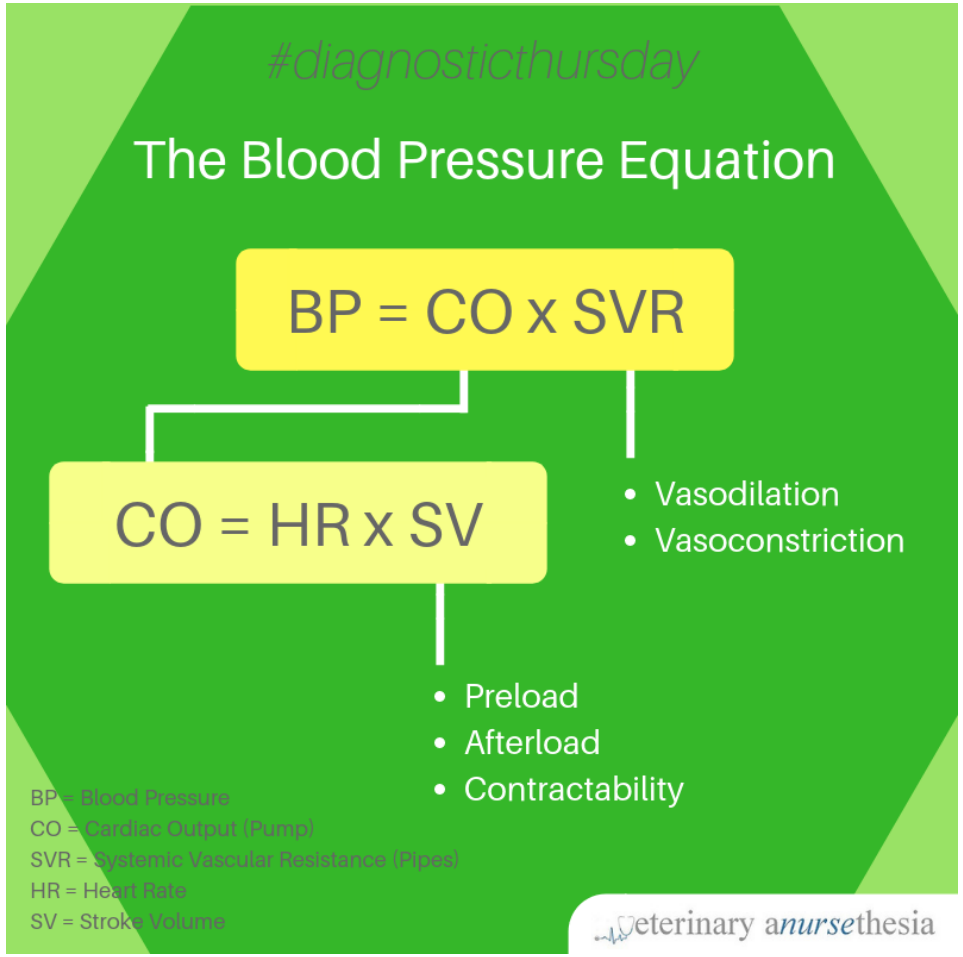
Heart Rate × Stroke Volume = C/O

Definition of blood pressure

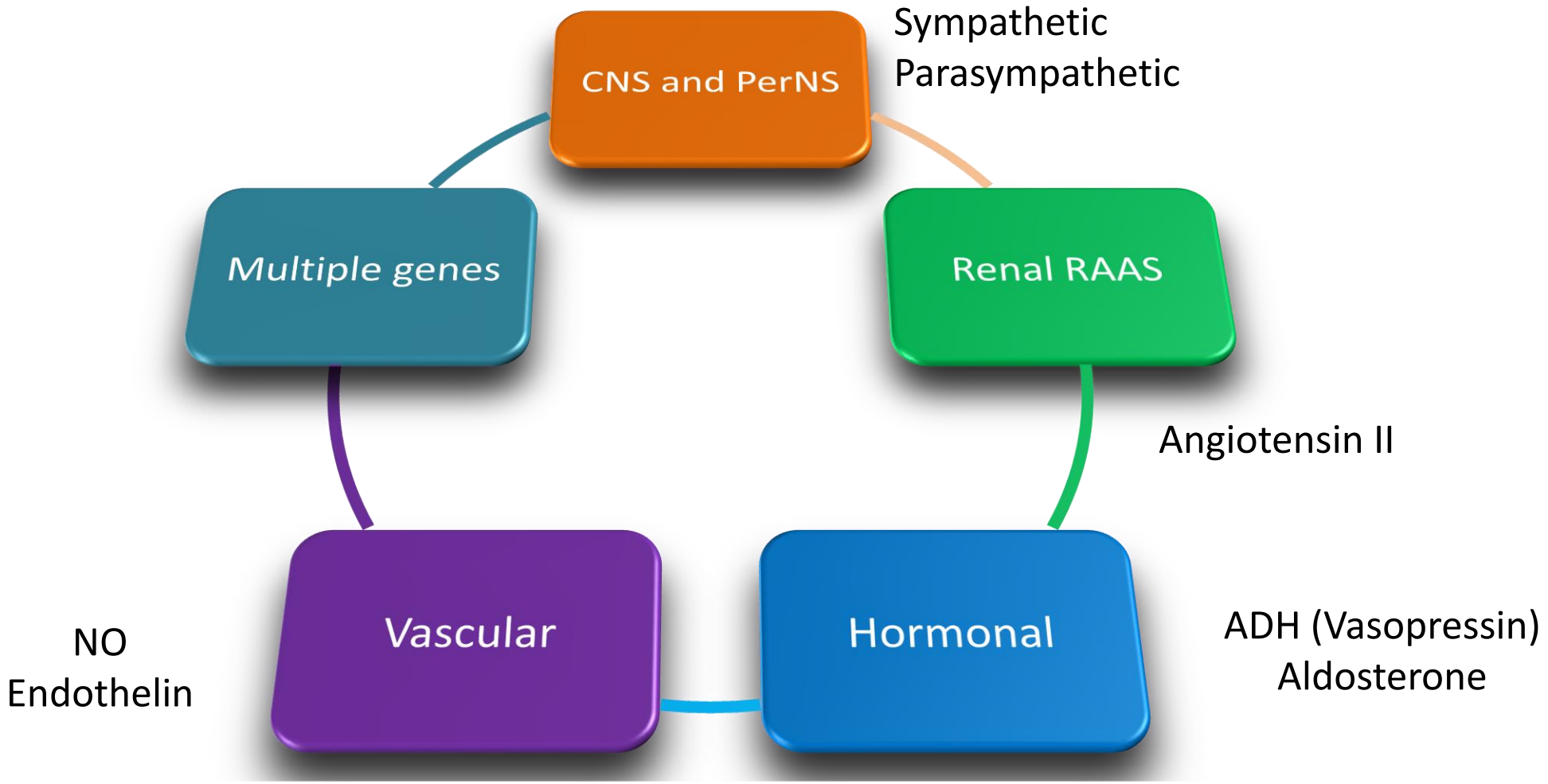


x

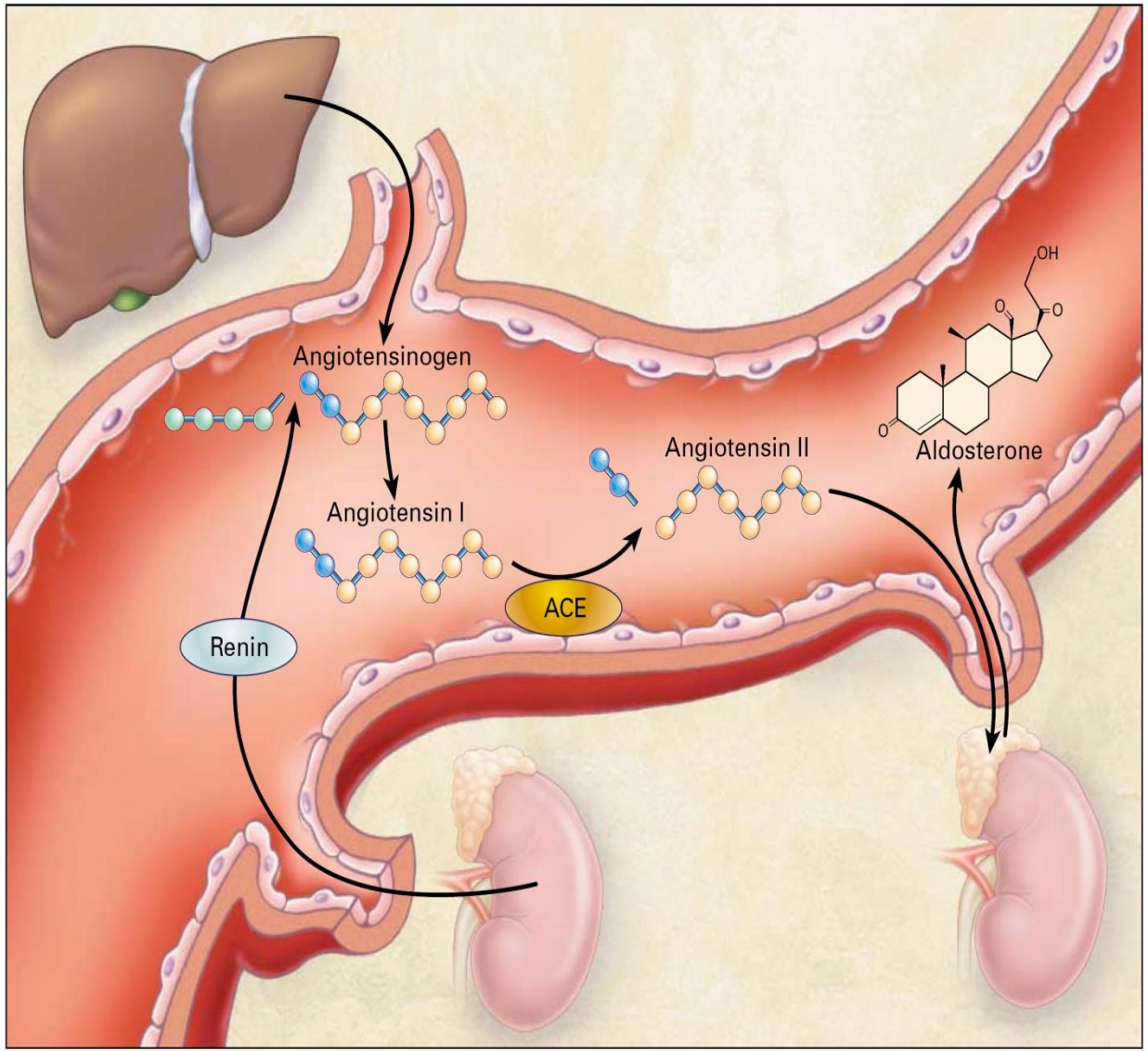
Blood pressure



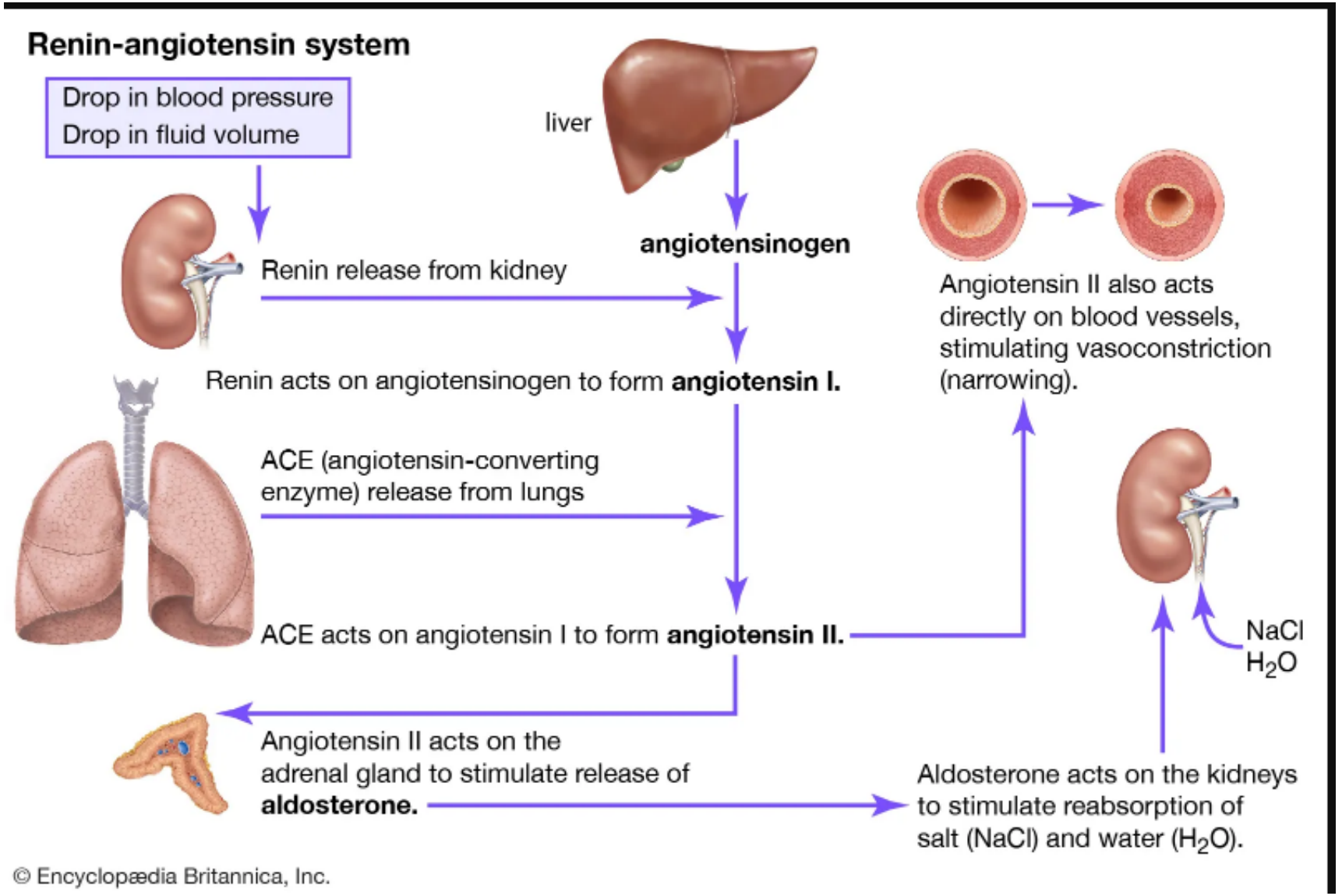
Systems involved in BP regulation



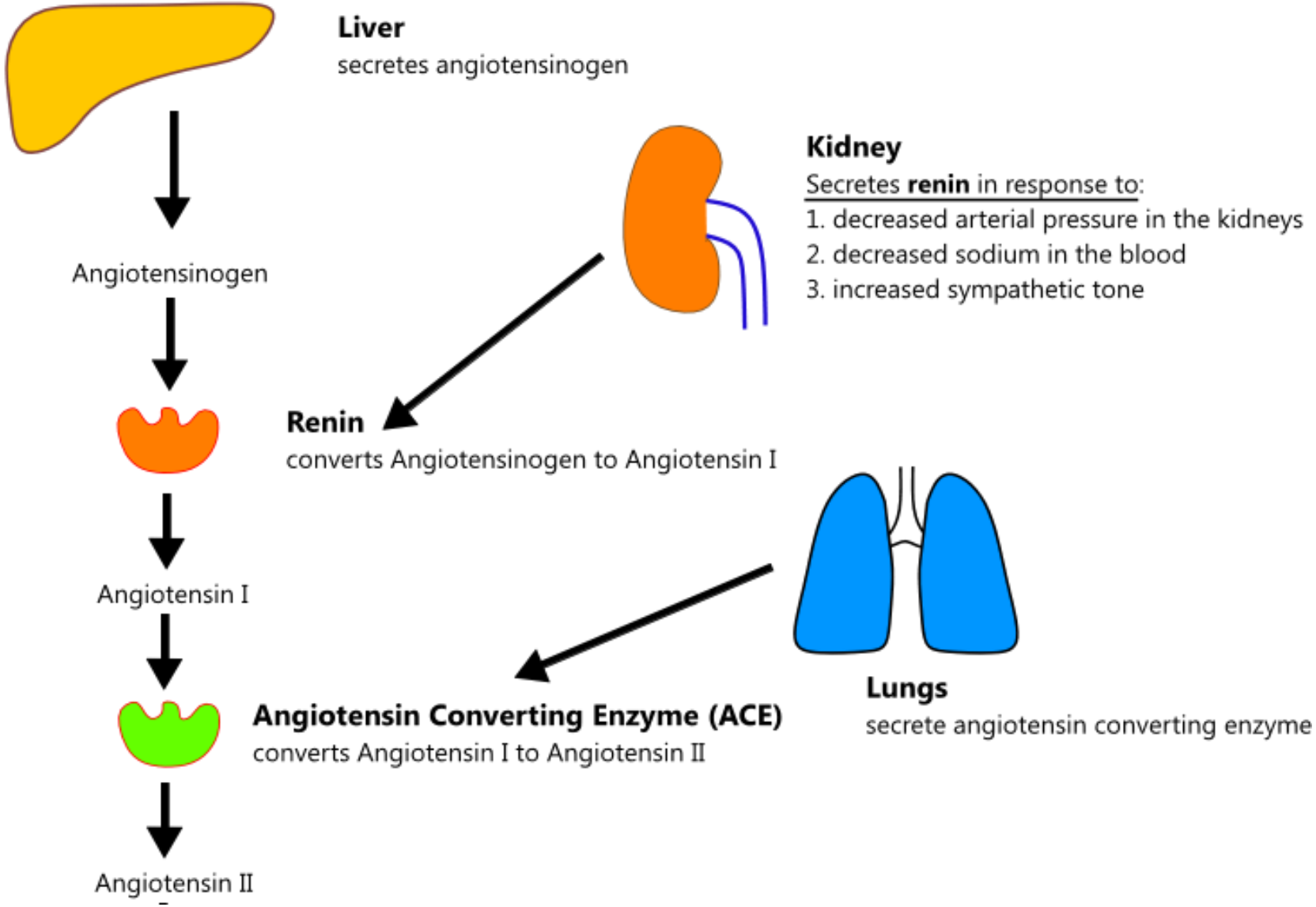
RAAS Activation



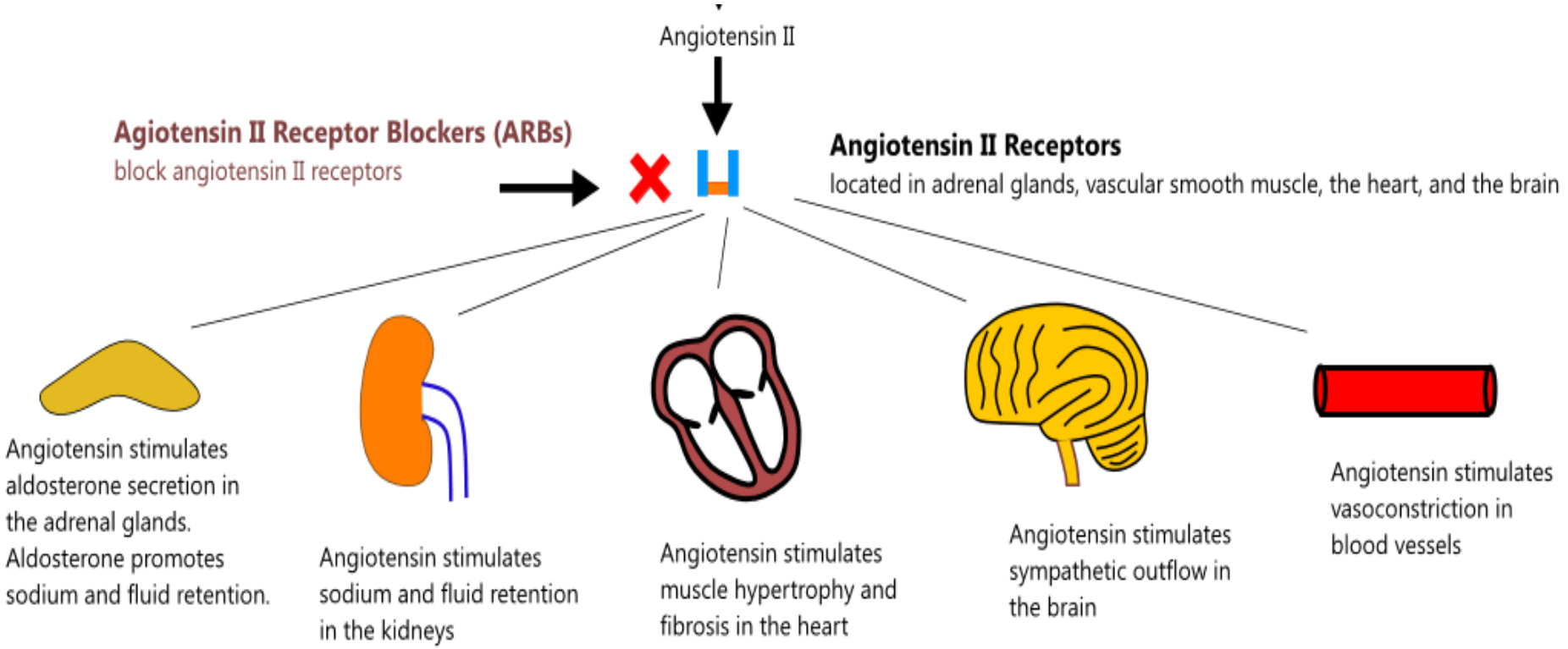
RAAS Activation



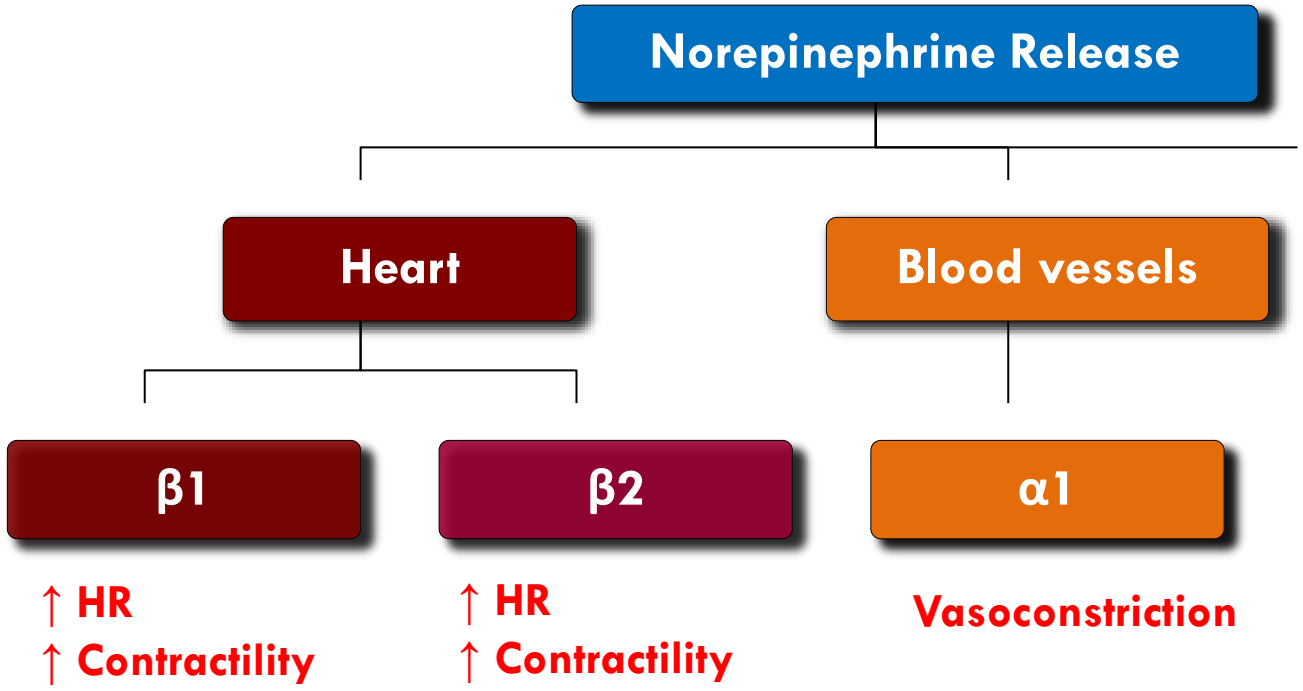
Revision- RAAS system



RAAS system cont.



Adrenergic Receptors in Heart and Kidneys



ADRENOR

Adrenor

Inj noradrenaline bitartrate 4mg/2ml for IV use

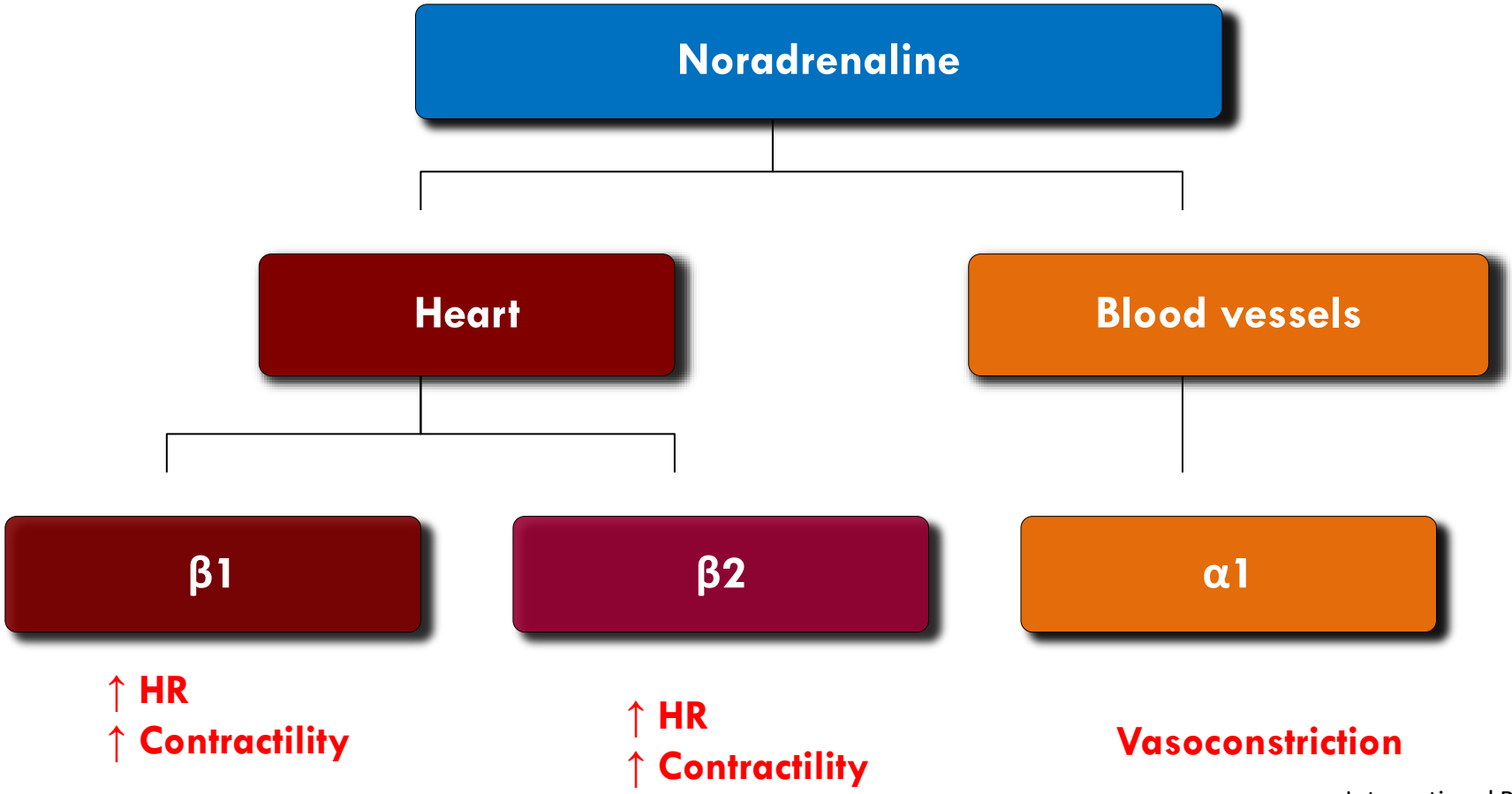
FOR IV INFUSION ONLY

Introduction

- A direct acting sympathomimetic agent

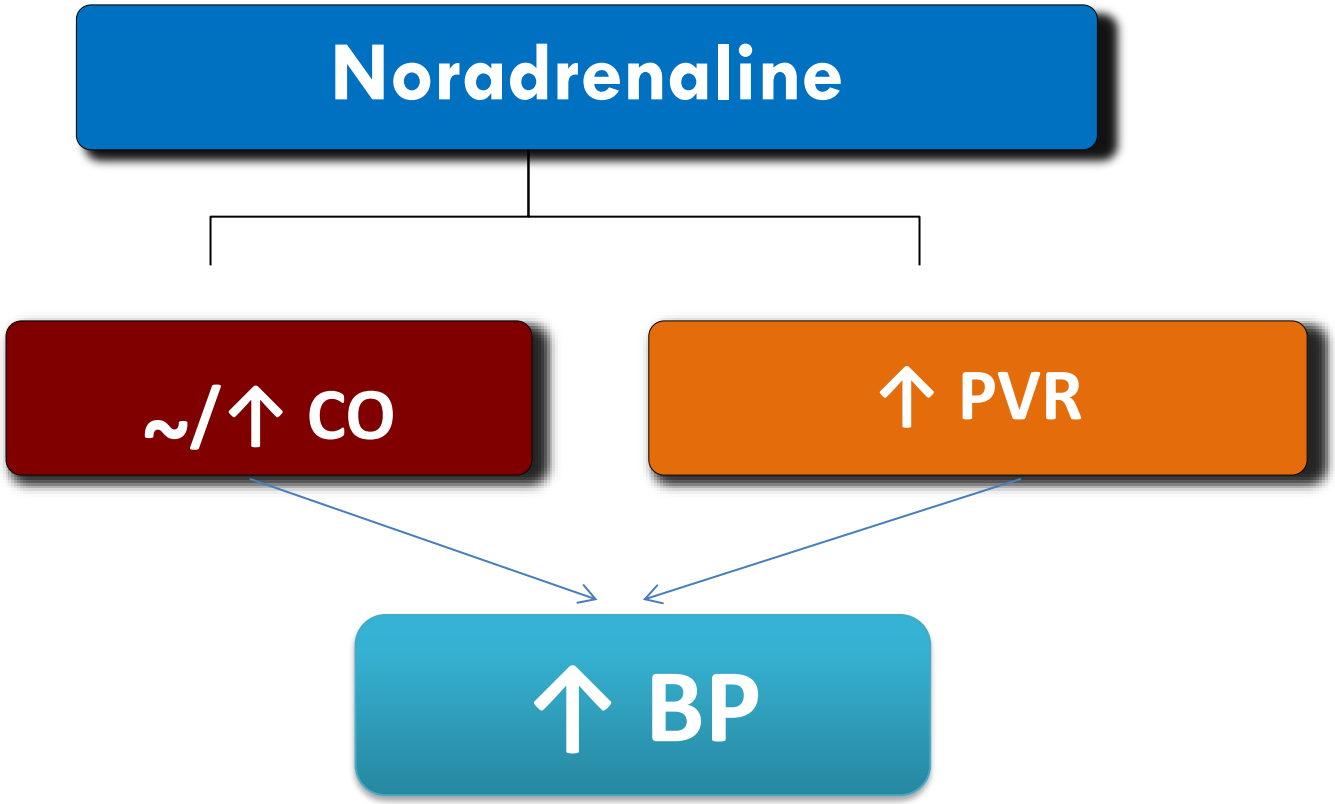
Mechanism of action

- It has pronounced effect on alpha receptors and little effect on beta receptors



Mechanism of action

- Adrenalin acts on both alpha and beta-adrenergic receptors



Indication

- Noradrenaline is indicated for the **emergency restoration of blood pressure** in cases of acute hypotension like SHOCK

Dilution

- Add 2 ml NA_b (2mg/ml) to 48 ml of 5% dextrose

4mg/50 ml i.e. 0.8 mg/10 ml

- Or

- Add 20 ml NA_b (2mg/ml) to 480 ml of 5% dextrose

40mg/500 ml i.e. 0.8 mg/10 ml

https://www.medicines.org.uk/emc/product/4115/smpc

Dilution

- Should be diluted in 5 % dextrose injection or 5 % dextrose and sodium chloride injections.
- These dextrose containing fluids are protection against significant loss of potency due to oxidation.
- Administration in saline solution alone is not recommended.

Dosage (i.v.)

- *Adults:*

Initial rate of infusion:

- The initial rate of infusion should be between 10 ml/hour and 20 ml/hour i.e. 0.8 to 1.6 mg/hr

The aim should be to establish a low normal systolic blood pressure (100-120 mm Hg)

https://www.medicines.org.uk/emc/product/4115/smpc

Titration of dose

Patient's Weight	Posology (µg/kg/min) Tartrate	Posology (mg/h) Tartrate	Infusion rate (ml/h)
60 kg	0.2	0.72	9
	0.5	1.8	22.5
	1	3.6	45
	2	7.2	90
70 kg	0.2	0.84	10.75
	0.5	2.1	26.25
	1	4.2	52.5
	2	8.4	105
80 kg	0.2	0.96	12
	0.5	2.4	30
	1	4.8	60
	2	9.6	120

https://www.medicines.org.uk/emc/product/4115/smpc

CPRESSIN AND CPRESSIN P

CPRESSIN PFS

CPRESSIN P inj

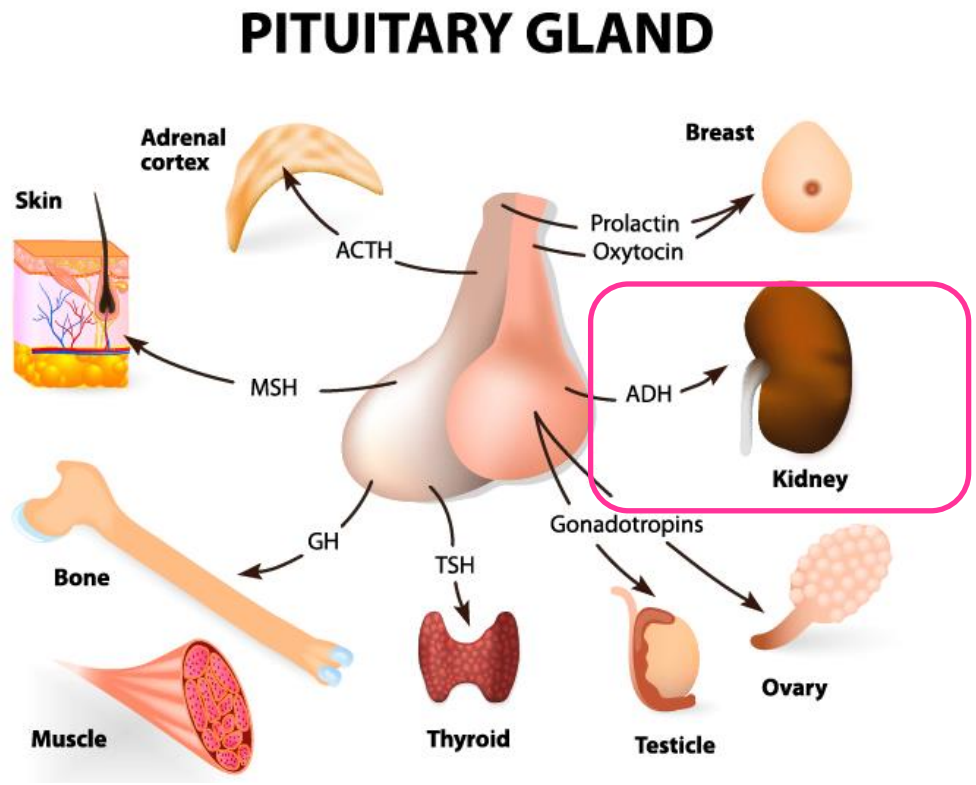
Vasopressin 40 IU/ml

Vasopressin 20 IU/ml

Introduction

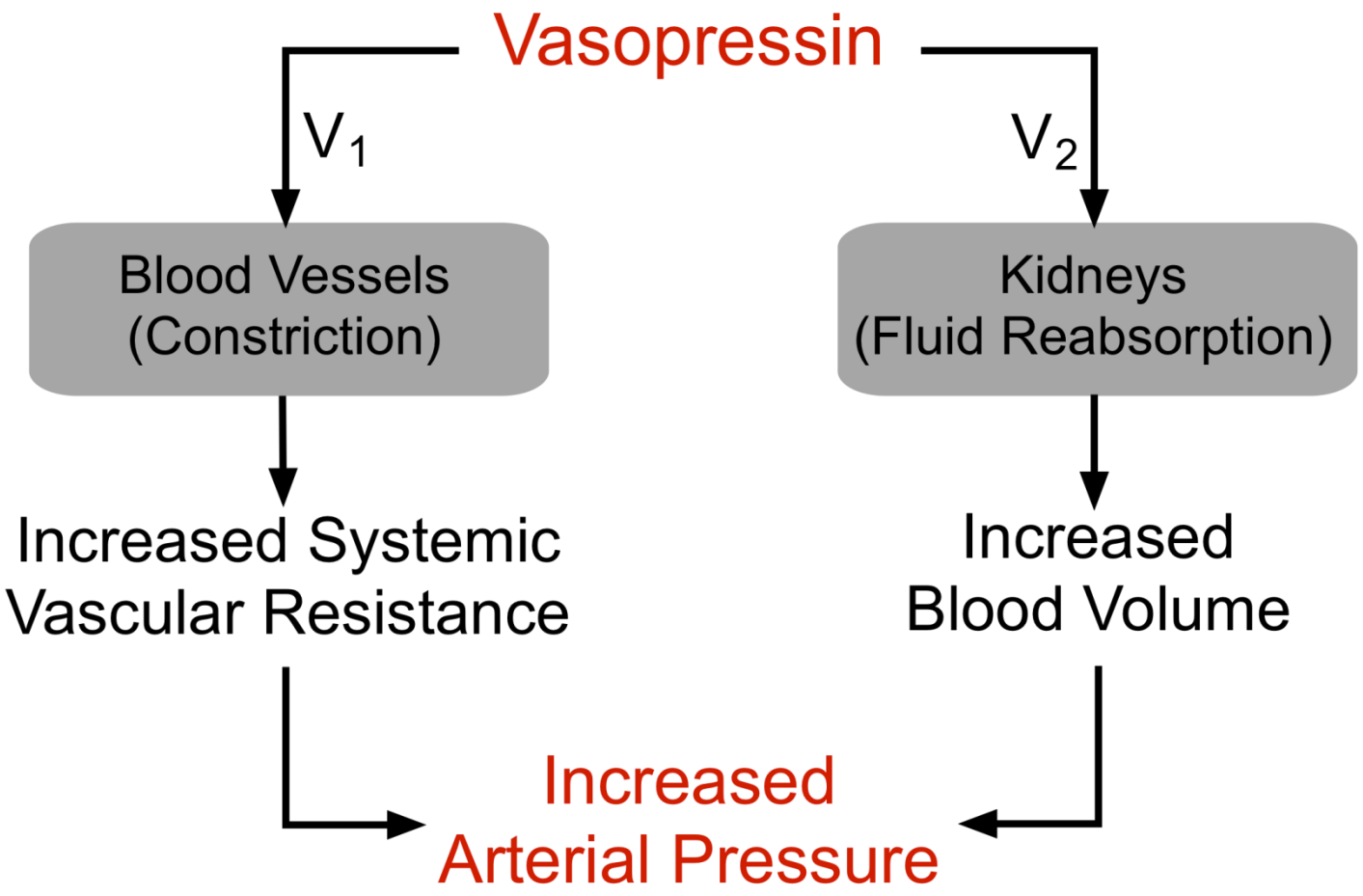
- A **hormone** having the properties of **vasoconstriction** and **ANTI-Diuresis**

- In physiology, it is also known as **Anti-Diuretic Hormone** which is secreted from Posterior part of pituitary gland



Martindale 38th Edn, pg 2642

Mechanism of action

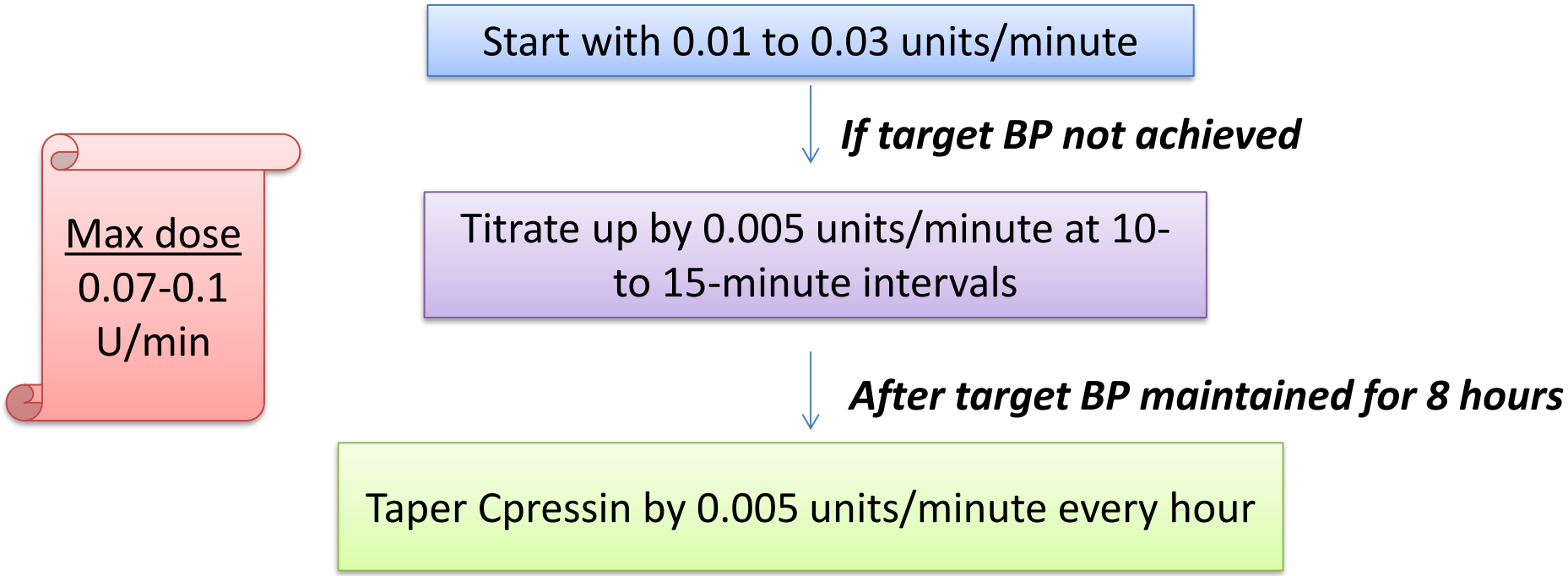


Indication

- To increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines (hormones produced by adrenal glands – e.g. NorEpinephrine).

Dosage (i.v.)

- Dilute Cpressin in normal saline (0.9% sodium chloride) or 5% dextrose prior to use.



Use in special population

- Pregnancy
  - No data available to establish safety
  - May produce tonic uterine contractions
- Lactation
  - No data available to establish safety
- Pediatric Use
  - Safety and effectiveness have not been established
- Geriatric Use
  - Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range

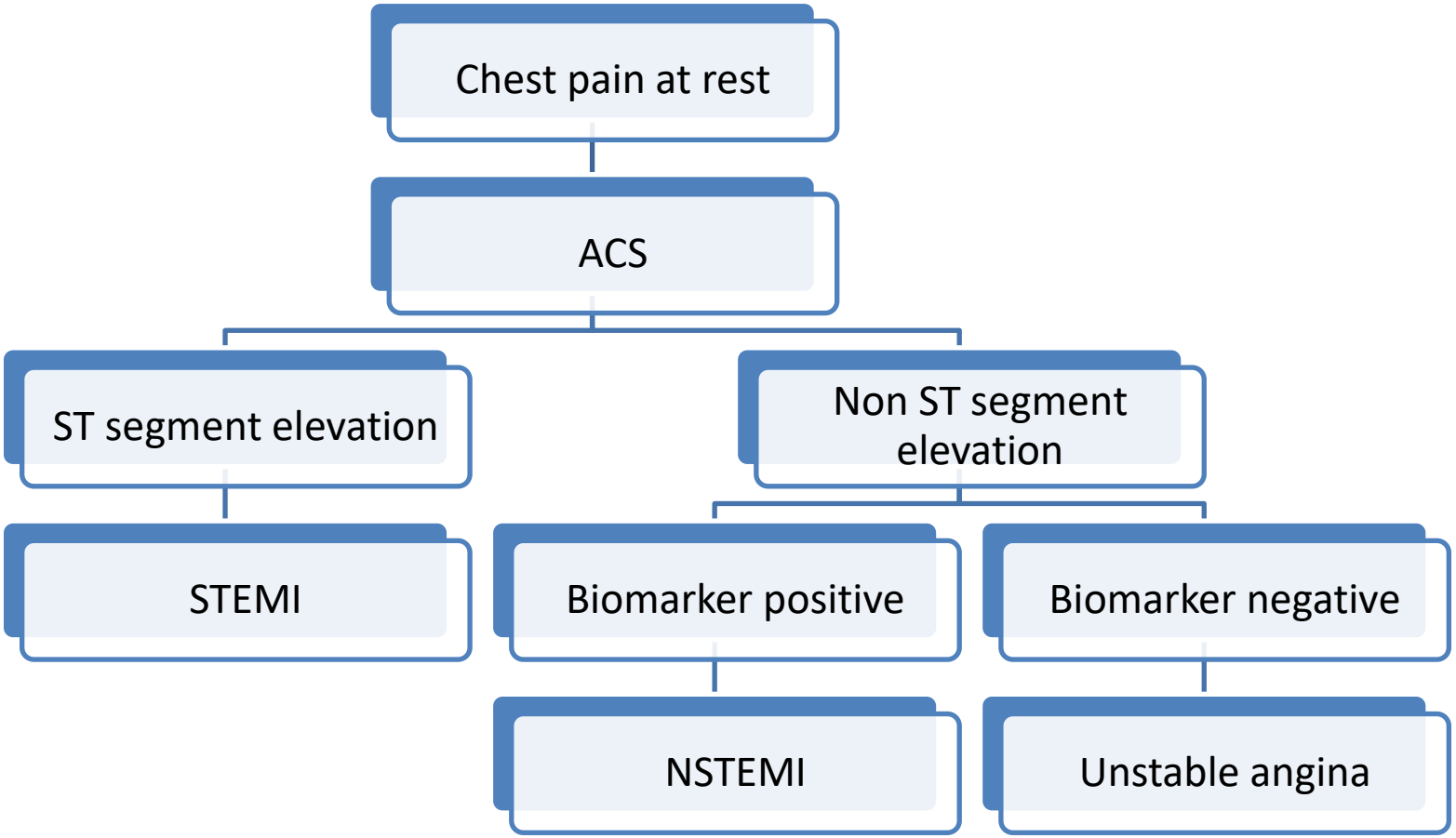
THANK YOU

ACUTE CORONARY SYNDROME (ACS)

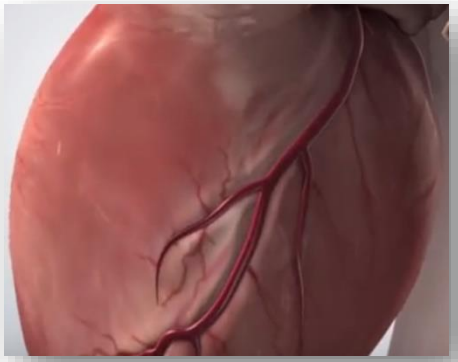
Myocardial infarction
Angina Pectoralis
Congestive heart failure
Cardiac surgeries and hypertension
Controlled hypotension
NITROCIN

ACUTE CORONARY SYNDROME (ACS)

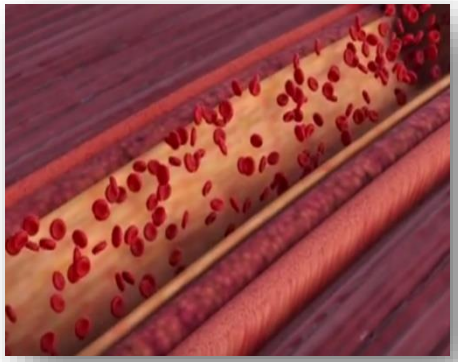
- Acute coronary syndrome describes a range of conditions associated with sudden, reduced blood flow to the heart



Coronary Artery Blockage

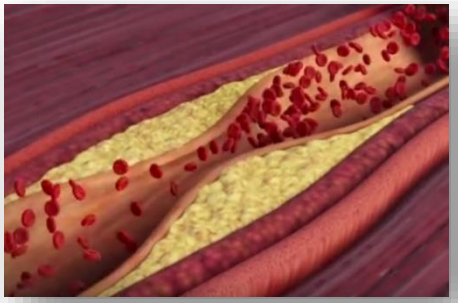


Normal Coronary Artery



Coronary artery with plaque partially blocking the blood flow

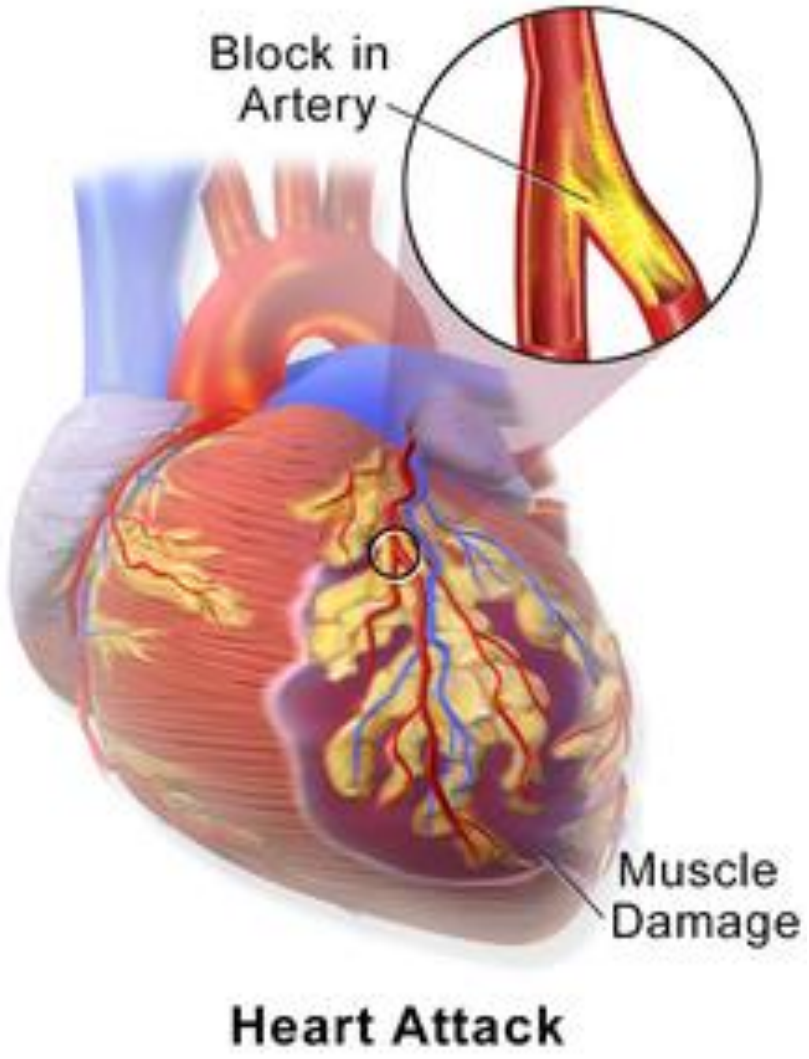
Rupture plaque with thrombus completely blocking the artery



MYOCARDIAL INFARCTION
STEMI AND NSTEMI

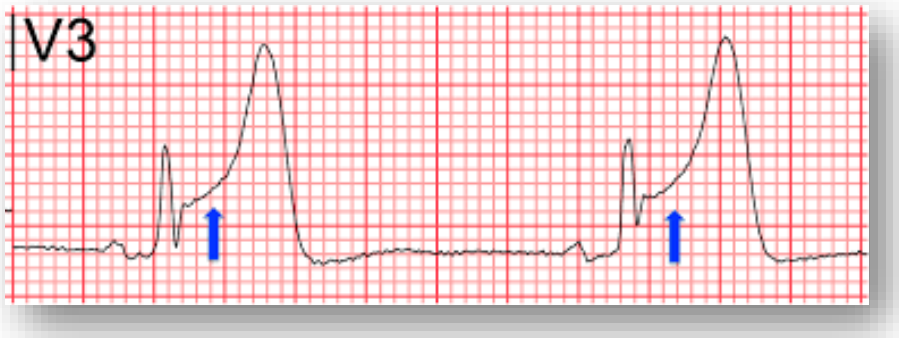
Myocardial infarction

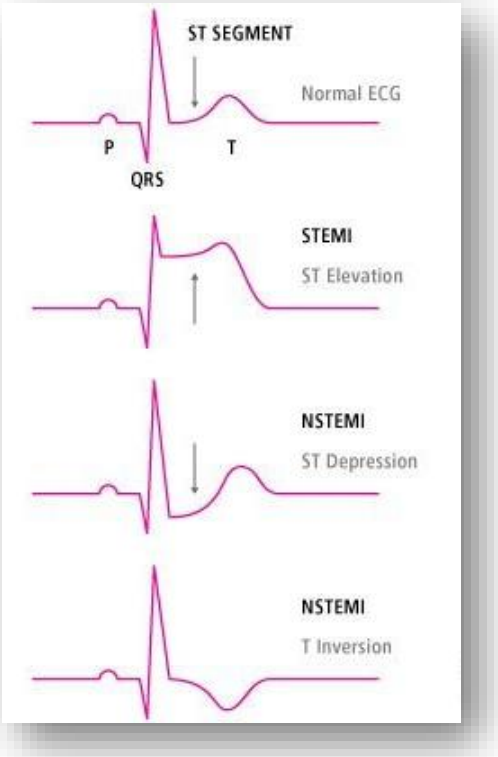
- Myocardial infarction (heart attack) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia)



ST-elevation myocardial infarction

- An acute ST-elevation myocardial infarction (STEMI) is an event in which transmural myocardial ischemia results in myocardial injury or necrosis





Epidemiology

- Coronary artery disease (CAD) is the leading cause of death
- Approximately 500,000-700,000 deaths related to CAD occur each year, making it the cause of death in an estimated one third of all deaths in the population for those older than 35 years.
- Approximately 1.5 million cases of myocardial infarction (MI) occur annually I
- Yearly incidence rate is approximately 600 cases per 100,000 people.
- Men have higher risk

https://emedicine.medscape.com/article/155919-overview#a6

Etiology

- Atherosclerosis is the disease primarily responsible for most acute coronary syndrome (ACS) cases. Approximately 90% of myocardial infarctions (MIs) result from an acute thrombus that obstructs an atherosclerotic coronary artery.

- Tobacco smoking
- Hypertension
- Drug abuse
- Obesity
- Stress
- Alcohol

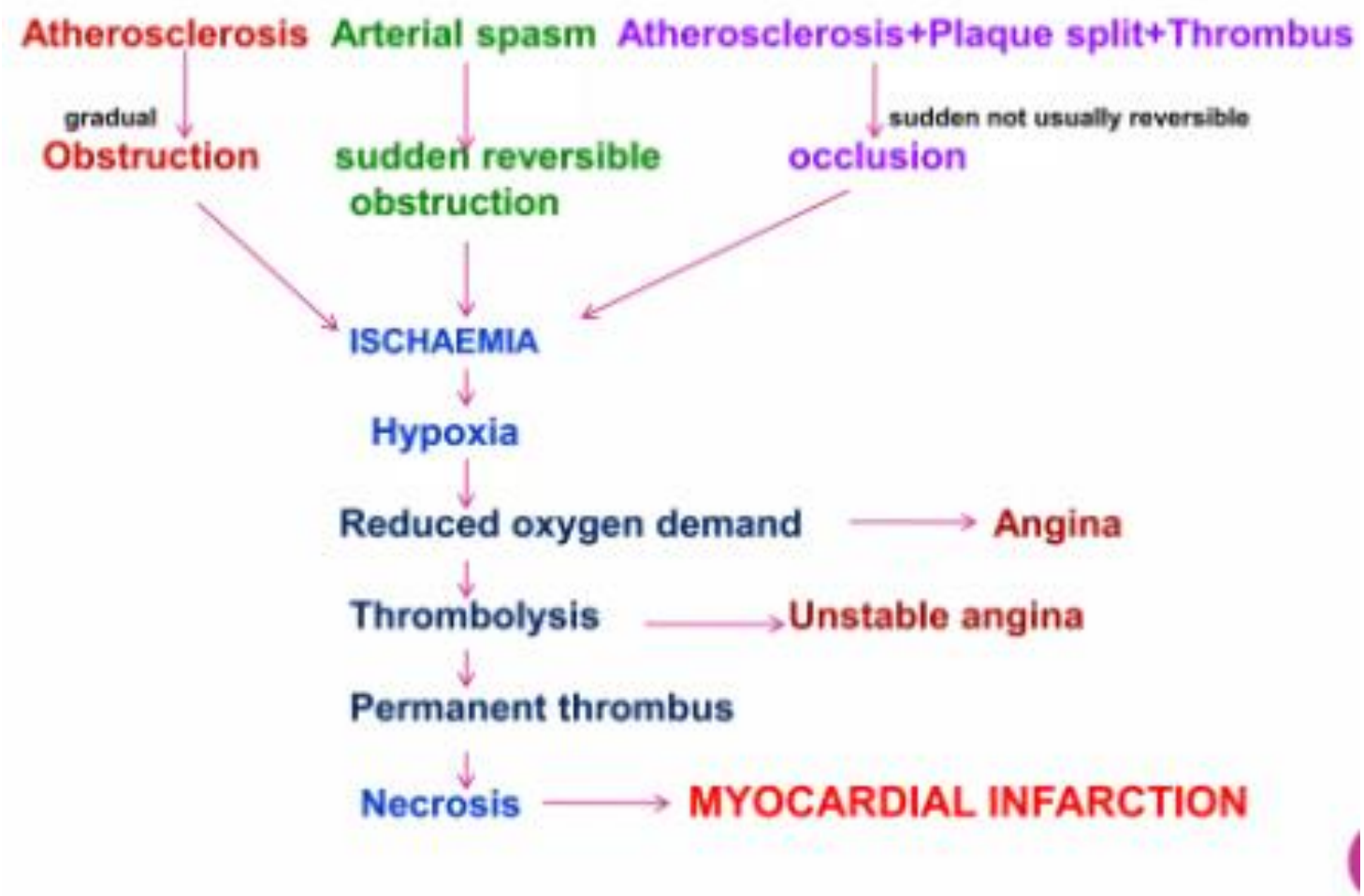
Risk factors for atherosclerosis

- Nonmodifiable risk factors
  - Age
  - Sex
  - Family history of premature coronary heart disease
  - Male-pattern baldness

Risk factors for atherosclerosis

- Modifiable risk factors
  - Smoking or other tobacco use
  - Hypercholesterolemia and hypertriglyceridemia, including inherited lipoprotein disorders
  - Dyslipidemia
  - Diabetes mellitus
  - Hypertension
  - Obesity (abdominal obesity)
  - Psychosocial stress
  - Sedentary lifestyle and/or lack of exercise
  - Type A personality
  - Elevated homocysteine levels

Pathophysiology



Diagnostic evaluation

- History
- Electrocardiogram
- Chest radiograph
- Cardiac biomarkers (eg, troponin)
- Echocardiogram
- Stress test

Prognosis

- Acute myocardial infarction (MI) is associated with a 30% mortality rate; about 50% of the deaths occur prior to arrival at the hospital.
- An additional 5-10% of survivors die within the first year.
- Approximately half of all patients with an MI are rehospitalized within 1 year of their index event.

- Overall, prognosis is highly variable and depends largely on the extent of the infarct, the residual left ventricular function, and whether the patient underwent revascularization.

Factors for better prognosis

- Successful early reperfusion (ST-elevation MI [STEMI] goals: patient arrival to fibrinolysis infusion within 30 minutes OR patient arrival to percutaneous coronary intervention [PCI] within 90 minutes)
- Preserved left ventricular function
- Short-term and long-term treatment with beta-blockers, aspirin, and angiotensin-converting enzyme (ACE) inhibitors

Presentation

- Chest pain
  - Most often in the early morning hours
  - Prodromal symptoms of fatigue, chest discomfort, or malaise in the days preceding the event
- Typical ST-elevation MI (STEMI) may occur suddenly without warning

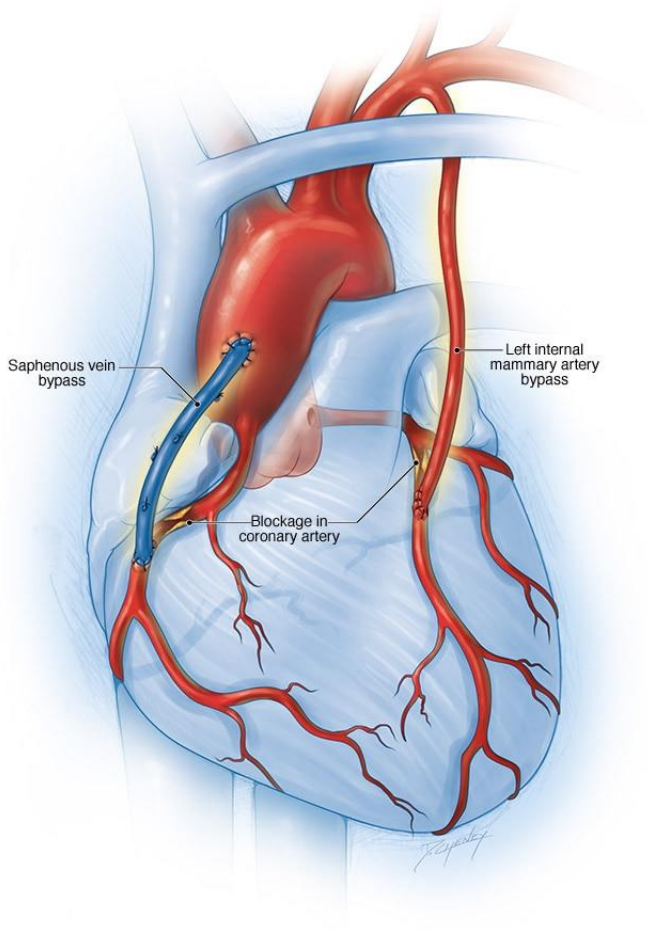
- Typical chest pain of acute MI
  - Usually intense and unremitting for 30-60 minutes.
  - Is retrosternal and often radiates up to the neck, shoulder, and jaws, and down to the left arm

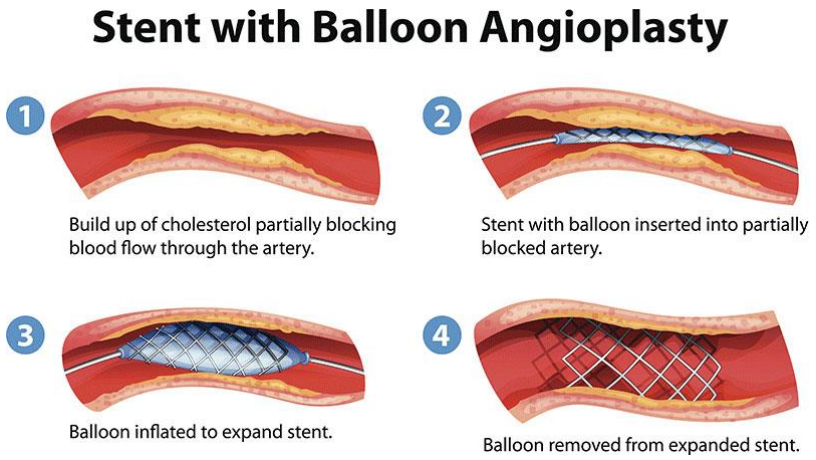
Other symptoms

- Anxiety, commonly described as a sense of impending doom
- Pain or discomfort in areas of the body, including the arms, left shoulder, back, neck, jaw, or stomach
- Lightheadedness, with or without syncope
- Cough
- Nausea, with or without vomiting
- Profuse sweating
- Shortness of breath
- Wheezing
- Rapid or irregular heart rate
- Fullness, indigestion, or choking feeling

Management

GOALS OF THERAPY: To reduce the risk of death and the extent of permanent cardiac injury associated with MI





- Coronary artery bypass graft (CABG)
- Angioplasty

Management of STEMI

- Initial management
  - Rapid selection and administration of reperfusion therapy (PCI or fibrinolysis)
- Medical therapy
  - Aspirin
  - **Nitrates (Nitroglycerin)**
  - Beta blockers (Atenolol, metoprolol)
  - Anticoagulation and additional antiplatelet agents (clopidogrel, ticagrelor)
  - Statins (Atorvastatin)
  - Morphine and oxygen

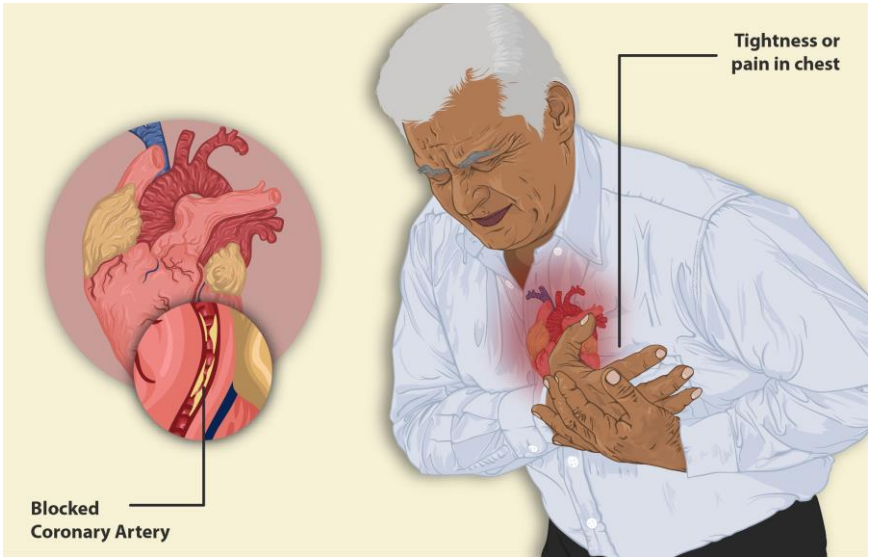
Place of nitrates: In patients with STEMI, nitrates can reduce the symptoms of chest discomfort and HF as well as treat hypertension

ANGINA PECTORIS

Angina pectoris

- Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand.

- Chest pain is a common presenting symptom (typically, chest pain) among patients with coronary artery disease (CAD).

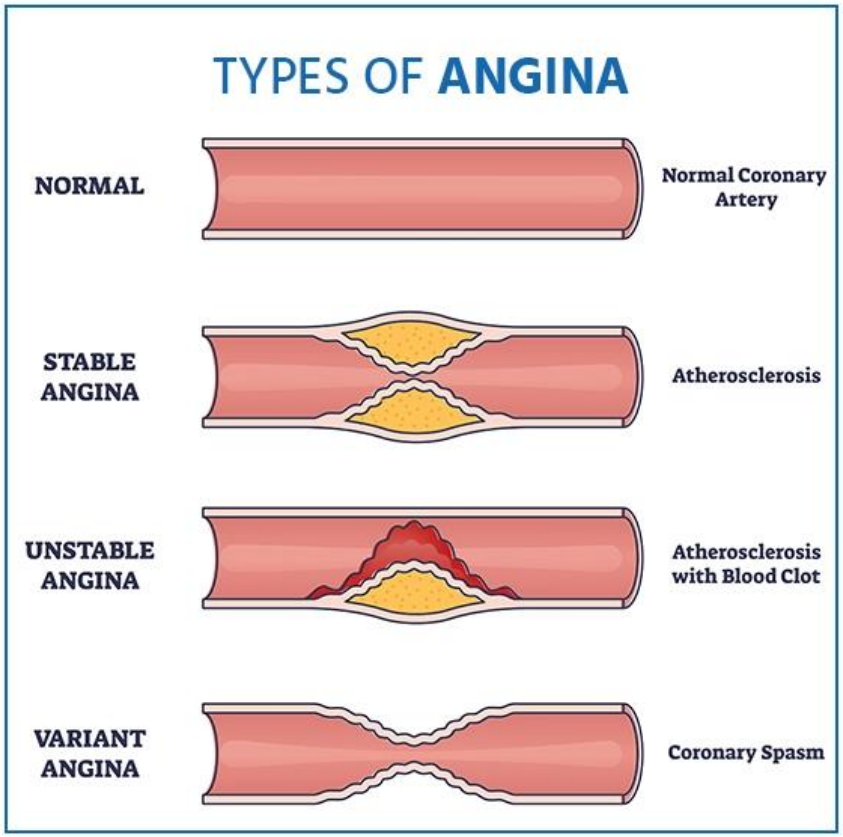


Prevalence

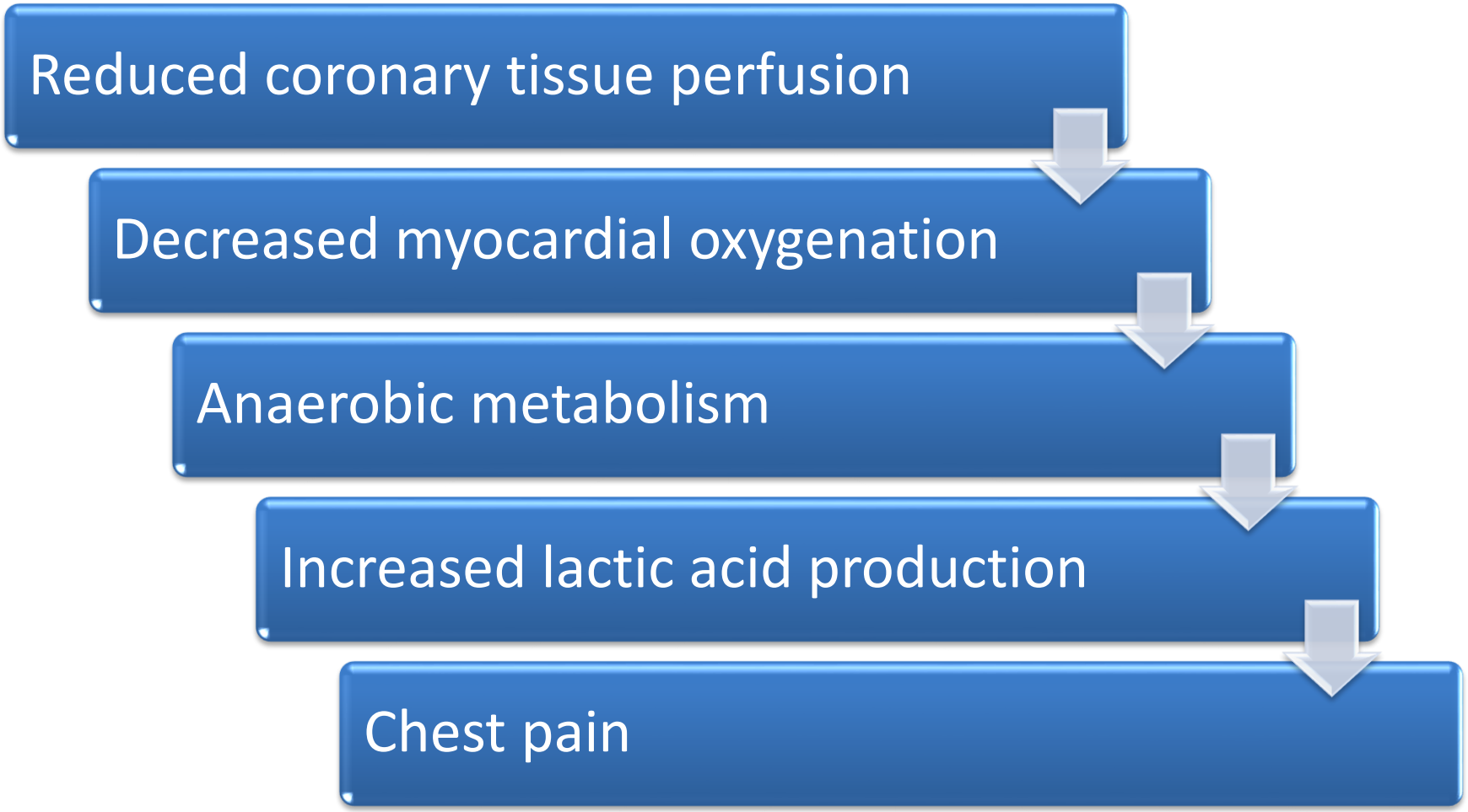
- Approximately 9.8 million are estimated to experience angina annually, with 500,000 new cases of angina occurring every year.

Types of angina

- Stable angina
  - fixed stenosis (demand ischemia)
- Unstable angina
  - thrombus (supply ischemia)
- Variant angina
  - Vasospasm (supply ischemia)
- Nocturnal angina
  - type of unstable angina



Pathophysiology



Signs and symptoms

- Retrosternal chest discomfort rather than frank pain
- Pain is described as a pressure, heaviness, squeezing, burning, or choking sensation
- Pain is localized primarily in the epigastrium, back, neck, jaw, or shoulders.
- Typical locations for radiation of pain are arms, shoulders, and neck.

Signs and symptoms (Cont..)

- Typically, angina is precipitated by exertion, eating, exposure to cold, or emotional stress.
- It lasts for approximately 1-5 minutes and is relieved by rest or nitroglycerin

RISK FACTORS

- MODIFIABLE RISK FACTORS:
  - Tobacco use
  - High blood cholesterol or triglyceride levels
  - Lack of exercise
  - Obesity
  - Stress
- NONMODIFIABLE RISK FACTORS:
  - Family history of heart disease
  - Older age
  - Diabetes
  - High blood pressure

CAUSES

Development of atherosclerosis

- Coronary artery disease is thought to begin with damage or injury to the inner layer of a coronary artery, sometimes as early as childhood.
- The damage may be caused by various factors, including:
  - Smoking
  - High blood pressure
  - High cholesterol
  - Diabetes or insulin resistance
  - Sedentary lifestyle

Diagnostic evaluation

- History
- Electrocardiogram
- Chest radiograph
- Cardiac biomarkers (eg, troponin)
- Echocardiogram
- Stress test

Management

- Beta blockers (decrease work load in heart)
  - Propranolol
- Calcium channel blockers (improve coronary blood flow)
  - Nifedipine
  - Verapamil
- Vasodilators (nitrates)
  - Glyceryl trinitrate
- Ranolazine is a newer addition

Place of nitrates: Glyceryl trinitrate injection may be used to treat unstable angina that is refractory to treatment with beta-blockers and sublingual nitrates

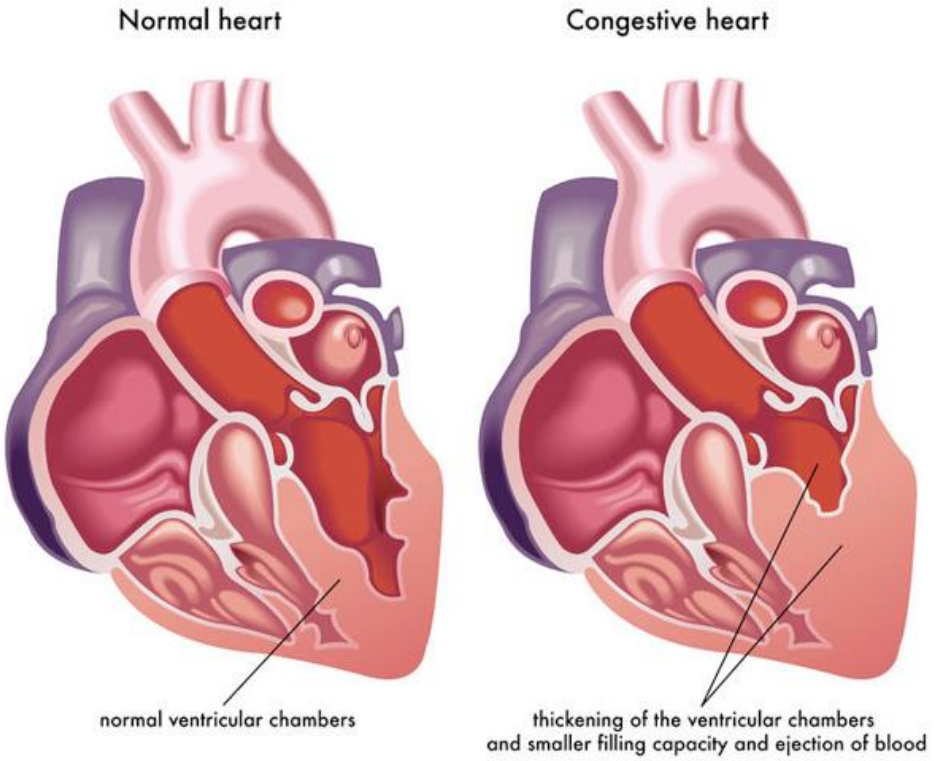
Prevention

- Antiplatelet therapy (Aspirin)
  - Prevention of blood clot forming
- Lipid-lowering therapy (Atorvastatin)
  - To reduce the risk of atherosclerotic
- ACE inhibitors or ARBs (Enalapril or losartan)
  - In subset of patients with chronic coronary syndrome
- Sodium-glucose cotransporter 2 inhibitors (Sitagliptin)
  - In patients with heart failure to reduce pre-load and after load
- Glucagon-like peptide 1 receptor agonists (Semaglutide)
  - In select patients with obesity

HEART FAILURE

Heart failure

- Heart failure is the pathophysiologic state in which the heart, via an abnormality of cardiac function (detectable or not), fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure



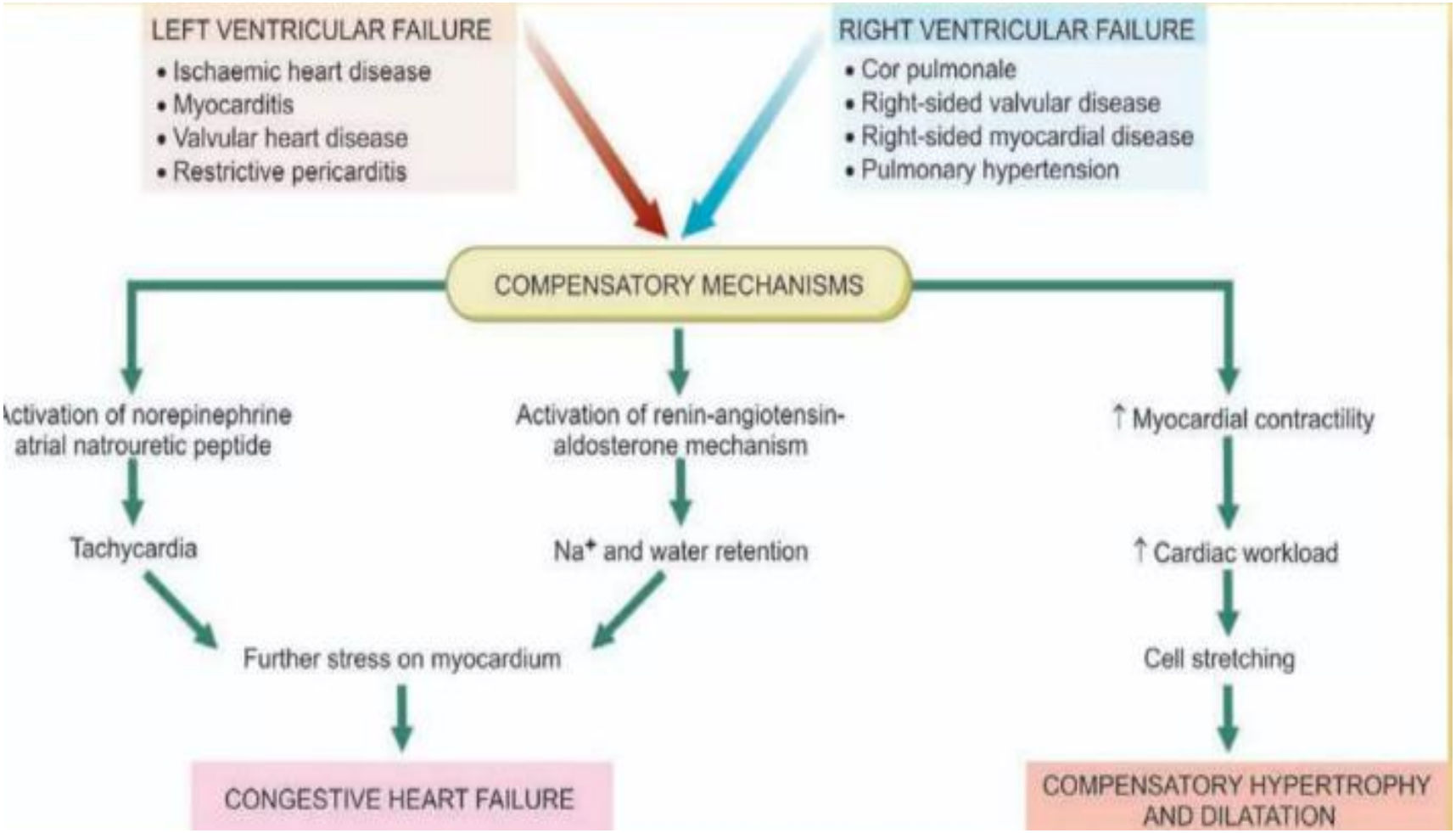
Signs and symptoms

- Symptoms
  - Fatigue
  - Weak ness
  - Shortness Of Breath on exertion
  - Shortness of Breath at Rest
  - Cough and wheezing
  - Anorexia (loss of appetite)
  - Paroxysmal nocturnal dyspnea
  - Nausea
  - Abdominal pain
  - Nocturia
- Signs
  - Pulmonary edema
  - Pleural effusion
  - Tachycardia
  - Narrow pulse pressure
  - Cardiomegaly
  - Peripheral edema
  - Jugular vein distension

Classification of heart failure

- The New York Heart Association (NYHA) classification for heart failure comprises four classes
  - Class I patients have no limitation of physical activity
  - Class II patients have slight limitation of physical activity
  - Class III patients have marked limitation of physical activity
  - Class IV patients have symptoms even at rest and are unable to carry on any physical activity without discomfort

Pathophysiology of heart failure



Diagnosis

- History
- Electrocardiogram
- Chest X-ray
- Echocardiogram
- Angiography
- Blood test

Management

- Treatment should address underlying causes (eg, intervention for coronary artery disease, intervention for symptomatic valve disease, therapy for treatable causes of cardiomyopathy) and associated conditions (eg, hypertension, diabetes mellitus, and thyroid dysfunction)

- Primary pharmacologic therapies
  - Renin-angiotensin system inhibitors/neprilysin inhibitors (Sacubitril-valsartan) (ARNI)
  - Beta blockers (Carvedilol)
  - Mineralocorticoid receptor antagonists (Spironolactone)
  - SGLT2 inhibitors (Dapagliflozin)
- Secondary pharmacologic therapies
  - Isosorbide dinitrate plus hydralazine
  - Ivabradine
  - Vericiguat
  - Digoxin

Place of nitrates: Glyceryl trinitrate may be used to treat unresponsive congestive heart failure secondary to acute myocardial infarction

CARDIAC SURGERIES AND HYPERTENSION

Perioperative hypertension

- Perioperative hypertension, defined as increased blood pressure around the surgery (pre-operative, intraoperative and post operative)
- It is a known risk factor for perioperative complications, including cardiovascular events
- Intraoperative hypertension poses a common clinical problem for anesthesiologists

EPIDEMIOLOGY OF HYPERTENSION IN THE OPERATING ROOM

- Patients with chronic hypertension sustain increased rates of both coronary artery disease and myocardial infarction
- They also have more episodes of myocardial ischemia unrelated to the presence of demonstrable coronary artery disease.

Clinical implications of perioperative hypertension

- CVS
  - Increased risk of cardiovascular events (e.g myocardial ischemia)
  - Increased post operative morbidity and mortality
  - Association with end organ damage such as renal failure
- CNS
  - Increased risk of stroke

Implication on CVS

- Increased BP
- Increased in afterload and myocardial oxygen demand
- Myocardial oxygen supply & demand imbalance
- Hypertrophied myocardium
- Decreased compliance & abnormal diastolic filling

Causes of arterial pressure elevation

- Activation of the renin-angiotensin system
- Endogenous and exogenous cathecholamines, and baroreceptor mechanisms

Cardiac surgeries associated with perioperative hypertension

- Coronary bypass surgery and aortic valve surgery are associated with significant intraoperative and post bypass hypertension.

Benefits of controlling perioperative hypertension during cardiac surgery

- To reduce bleeding from suture lines,
- Improve visualization and operating conditions
- Reduce myocardial wall tension and subsequent oxygen consumption

ANESTHESIOLOGY CLINICS OF NORTH AMERICA. VOLUME 17 * NUMBER 3 * SEPTEMBER 1999

Treatment of perioperative hypertension

- Vasodilators
  - Clevidipine
  - Enalaprilat
  - Fenoldopam
  - Hydralazine
  - Nicardipine
  - Nitroglycerin (glyceryl trinitrate)
  - Sodium nitroprusside
- Adrenergic inhibitors
  - Esmolol
  - Labetalol
  - Metoprolol
  - Phentolamine

www.uptodate.com

CONTROLLED HYPOTENSION

Controlled hypotension

- Controlled hypotension is a technique that decreases arterial pressure until hypotension is reached to reduce blood loss and the need for transfusion during surgery, and to improve the quality of the surgical field

Controlled hypotension & Surgeries

- Surgeries of low hemorrhagic potential to ensure a clear surgical field
  - surgery of the middle ear
  - endoscopic sinus micro-surgery
  - plastic and reconstructive microsurgery
  - ophthalmologic surgery
  - neurosurgery

Controlled hypotension & Surgeries

- Surgeries of moderate or extreme hemorrhagic potential to decrease the requirement for transfusion
  - orthopedic surgery
  - urologic surgery
  - cardiovascular surgery
  - hepatic transplantation

Objective of controlled hypotension

- Fall in systolic blood pressure (SBP) to 80–90mm Hg, or mean arterial pressure (MAP) to 50–65 mm Hg in patients without hypertension, or a fall of 30% of MAP in patients with hypertension

Limits and Complications of controlled hypotension

- Controlled hypotension could result in tissue hypoxia by reducing or suppressing the microcirculatory autoregulation of the vital organs and by inhibiting the autonomic nervous system

Goal of controlled hypotension

- To maintain a pressure sufficiently low to allow a reduction in bleeding without suppressing the microcirculatory autoregulation of the vital organs (i.e. brain, heart or kidney)

Drugs used in controlled hypotension during surgery

- Anaesthetics
- Vasodilators
  - Sodium nitroprusside
  - Nitroglycerin
  - Adenosine
  - Alprostadil
  - Calcium channel antagonists: nicardipine, diltiazem
  - Fenoldopam
- Autonomic nervous system inhibitors
- ACE inhibitors

Nitrocin

Inj 5mg/ml

Introduction

- NTG is a vasodilator

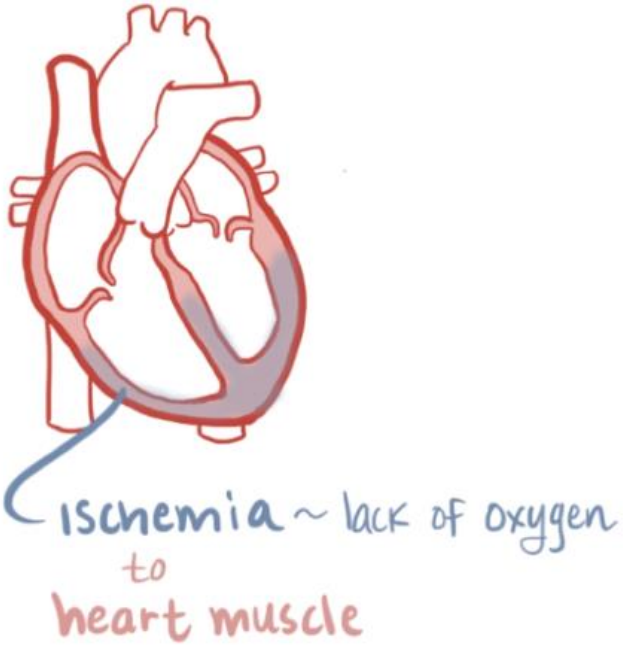
Martindale 38th Edn, pg 1392

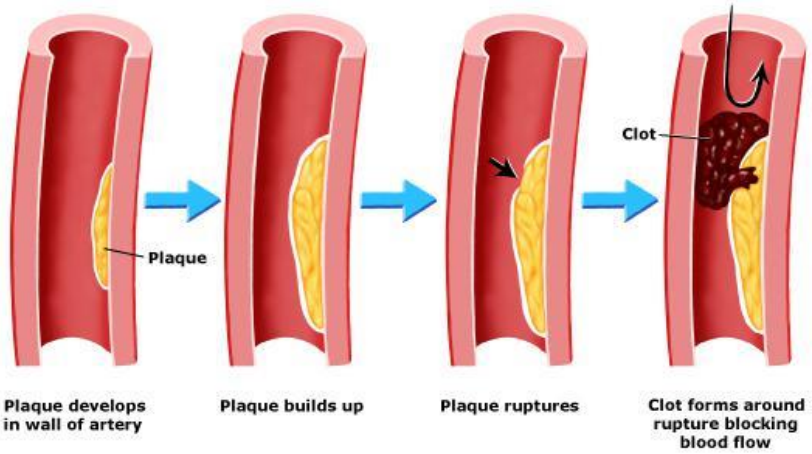
Indication

- Unresponsive **congestive heart failure** (supportive)
- **Unstable angina**
- Control of **hypertensive episodes and/or myocardial ischaemia** during and after cardiac surgery

Angina

Reduced blood flow to heart

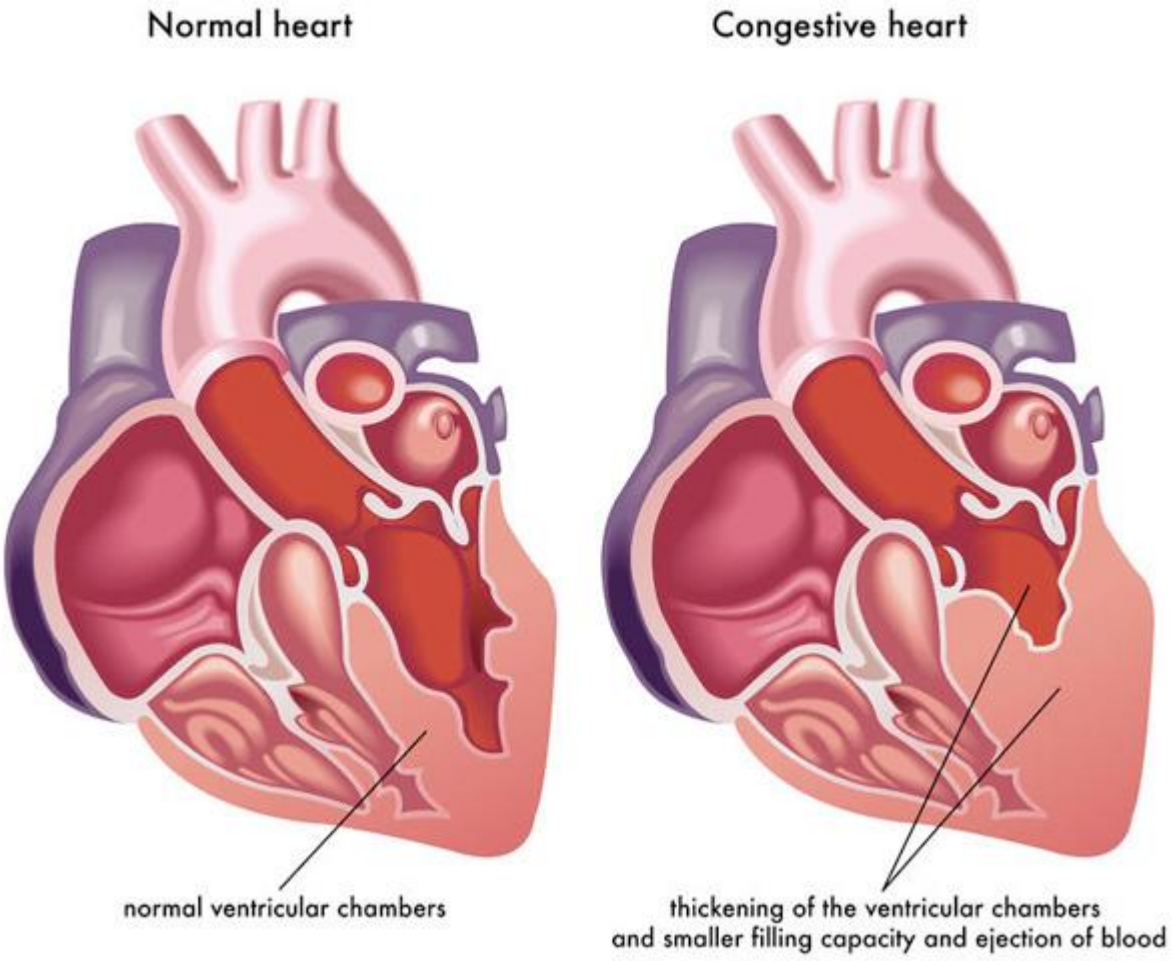




Chest pain, pressure, often due to not enough blood flow to the heart muscle as a result of **obstruction or spasm of the coronary arteries**

Main cause: Atherosclerosis: Plaque in the blood vessel

Congestive Heart Failure

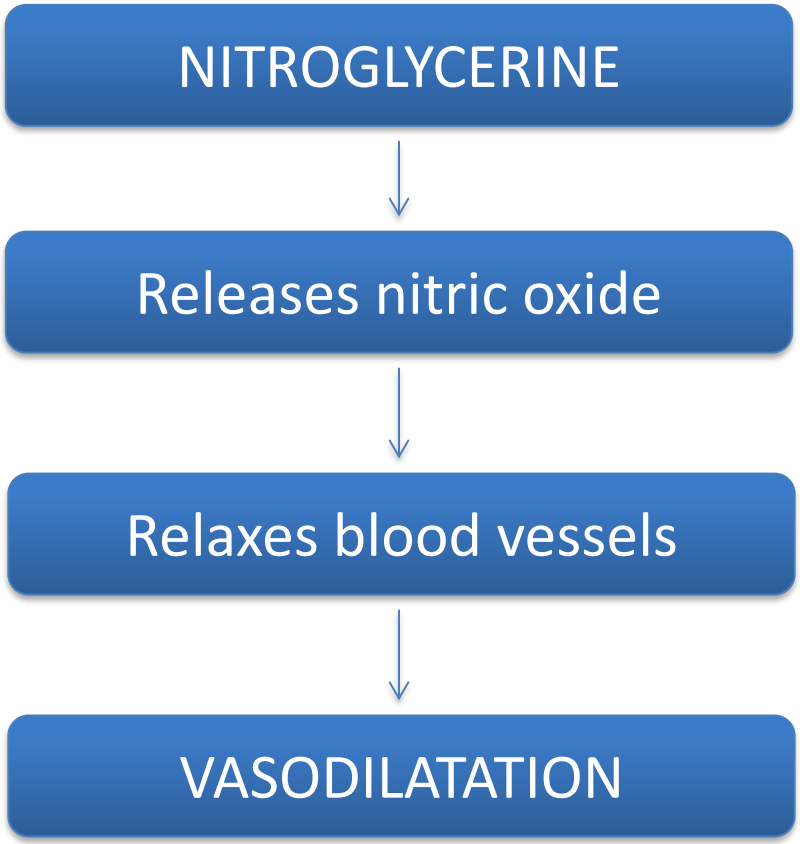


When the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs

Causes:

- myocardial infarction (heart attack)
- High blood pressure
- Atrial fibrillation
- Valvular heart disease

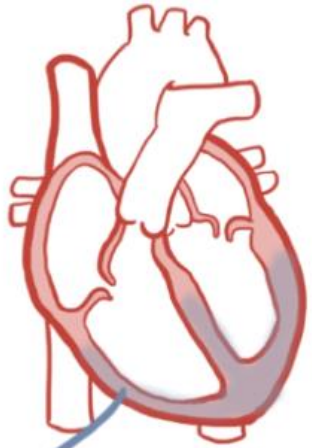
Mechanism of action



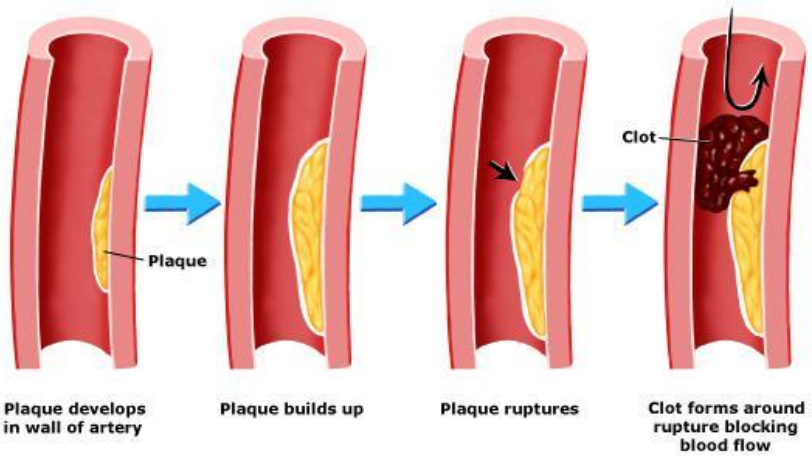
Martindale 38th Edn, pg 1392

MOA in Angina

Reduced blood flow to heart



ischemia ~ lack of oxygen to heart muscle



Dilatation of coronary arteries

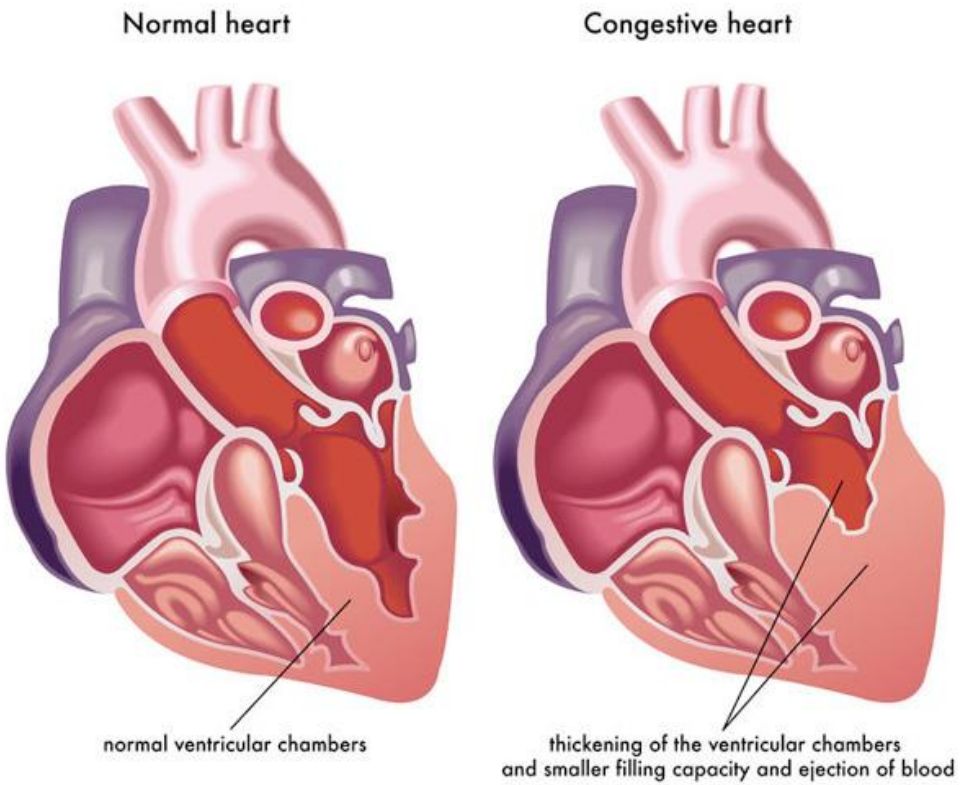
↓

Blood flow to myocardium improve

↓

Relief from symptoms

Congestive Heart Failure



Dilatation of coronary arteries

↓

Blood flow to myocardium improve

↓

Heart works more efficiently

When the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs

Dosage (i.v.)

Unresponsive congestive heart failure:

Starting dose is **20 - 25 mcg/min**. Range 10 mcg/min-25 mcg/min every 15 - 30 minutes until the desired effect is obtained

Unstable angina:

An initial dose of **10 mcg/min** is recommended with increments of 10mcg/min being made at approximately 30 minute intervals according to the needs of the patient

Myocardial ischaemia (Perioperative)

Start with a dose of **15 - 20 mcg/min**, with subsequent increments of 10 - 15 mcg/min until the required effect is obtained

https://www.medicines.org.uk/emc/product/6296/smpc

THANK YOU

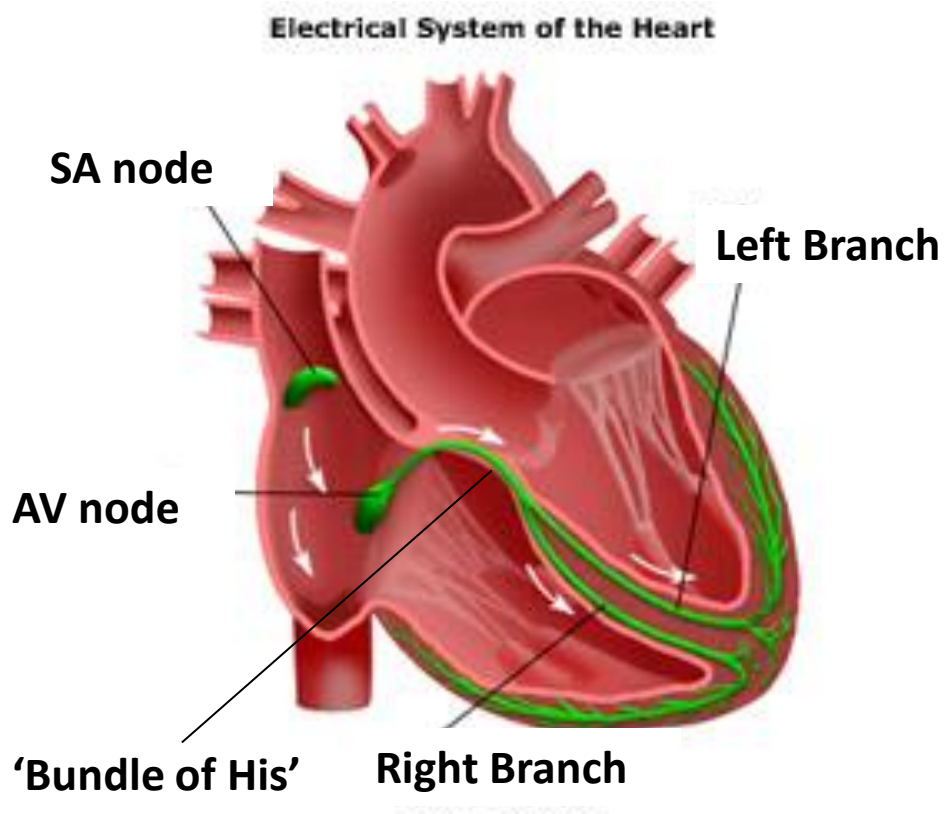
BRADYCARDIA
ATRIO-VENTRICULAR BLOCK

Sinus Bradycardia

- Sinus bradycardia can be defined as a sinus rhythm with a resting heart rate of 60 beats per minute or less.
- However, few patients actually become symptomatic until their heart rate drops to less than 50 beats per minute.

Normal Rhythm of the HEART

- 60-100 beats/minute & Originate from SA node



Impulse generates from SA node

↓

Spreads in both Atria

↓

Atria contracts

↓

Impulse moves to AV node

↓

It travels thorough 'Bundle of His'

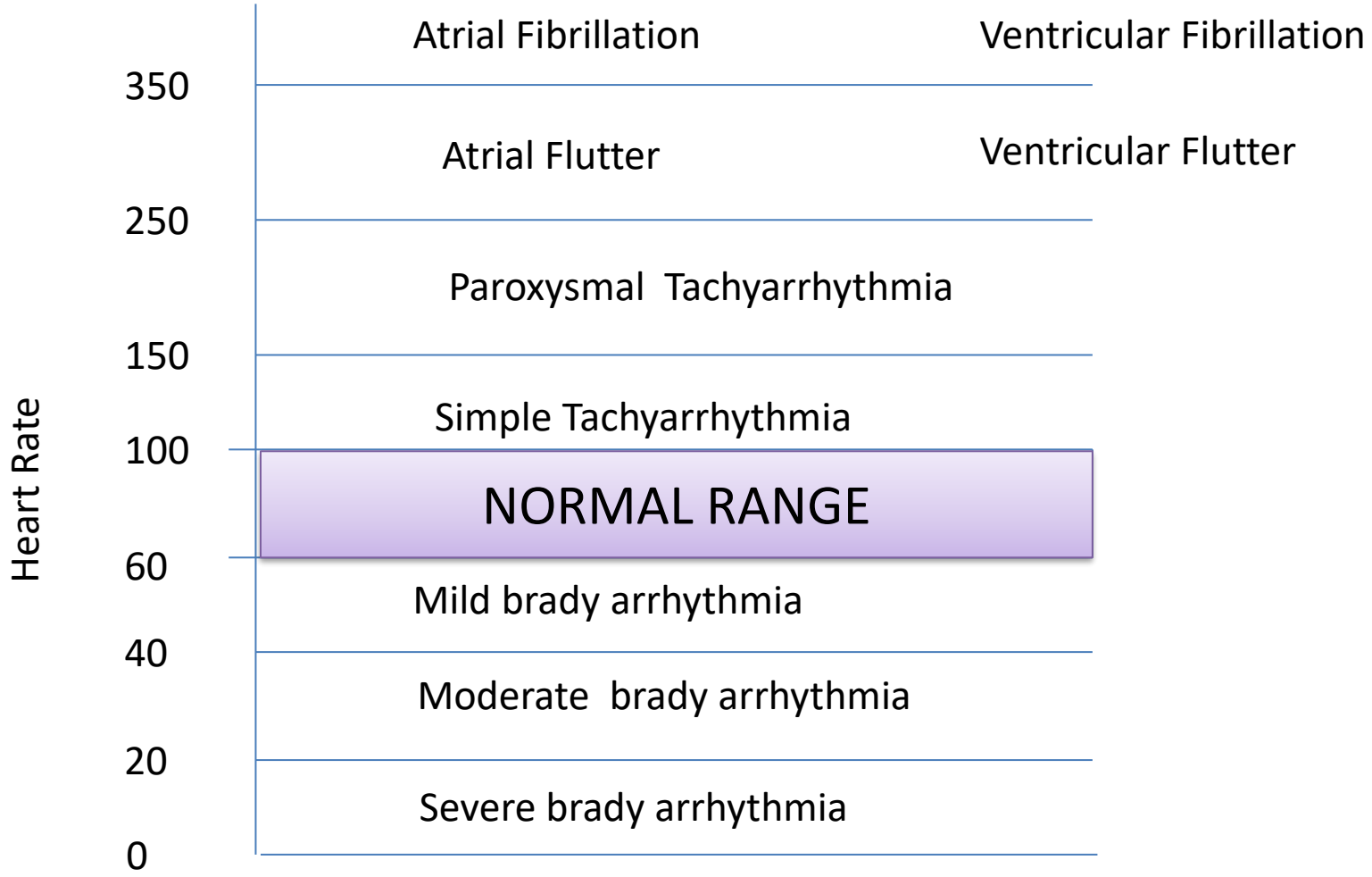
↓

Splits through Right and Left Branches

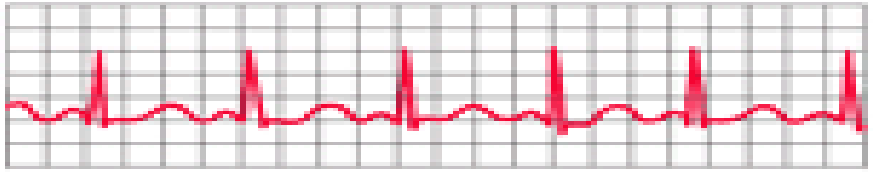
↓

Contraction of both Ventricles

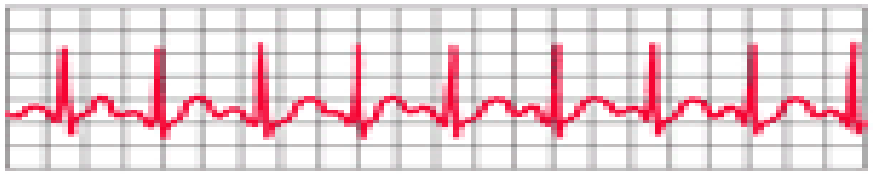
Classification – depending on HR



Normal Heartbeat

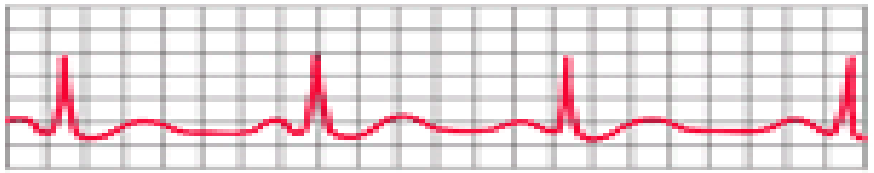


Fast Heartbeat



Tachycardia

Slow Heartbeat

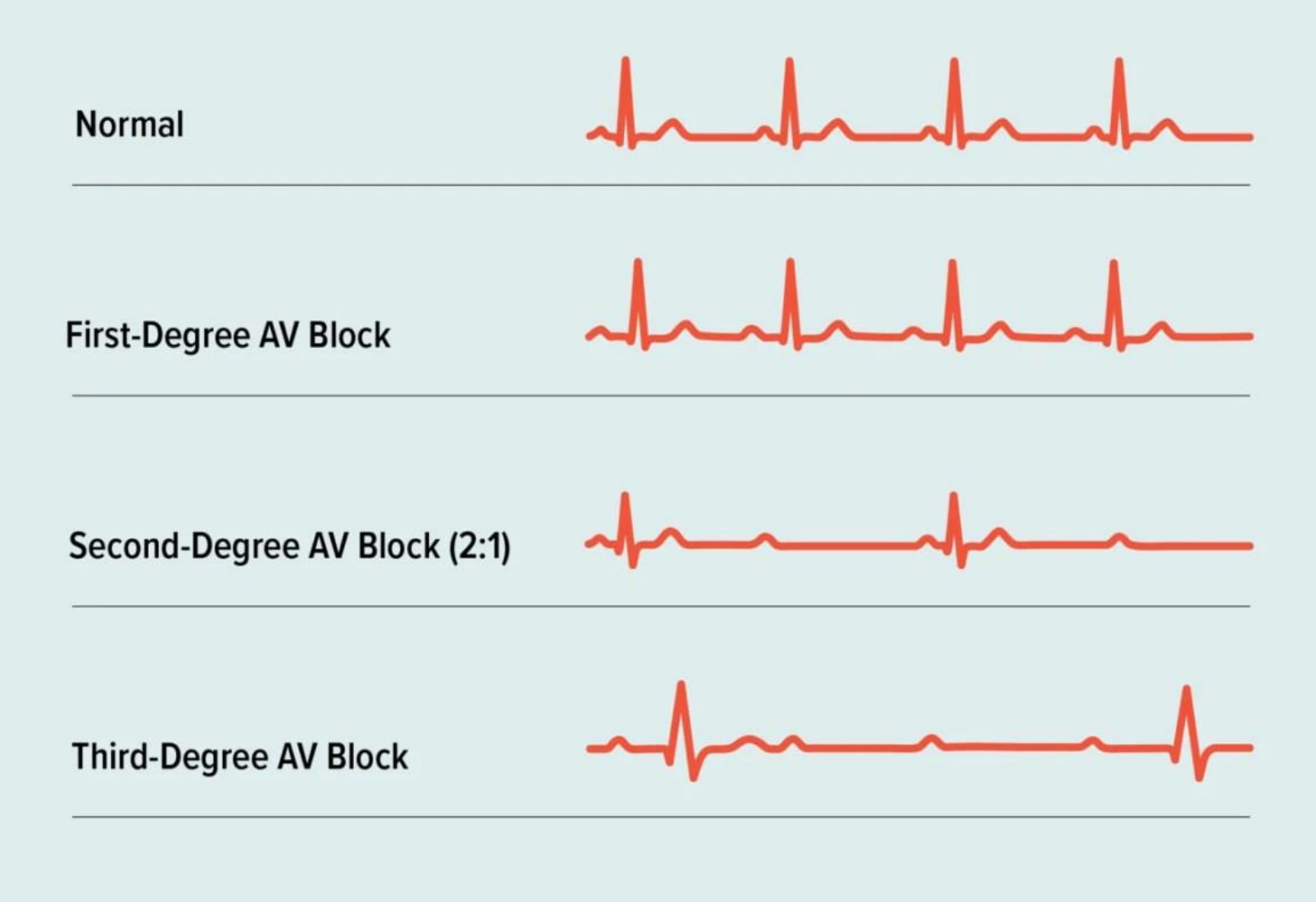


Bradycardia

Atrio-ventricular block

- Atrioventricular (AV) block is an interruption or delay of electrical conduction from the atria to the ventricles due to conduction system abnormalities in the AV node or the His-Purkinje system

Types of AV block



Signs and symptoms

- First-degree AV block
  - Generally asymptomatic
  - Excessive delay causes dyspnea, weakness, or dizziness
- Second-degree AV block
  - Can be asymptomatic
  - Palpitations, weakness, lightheadedness, or syncope
  - Manifests on physical examination as **bradycardia**
- Third-degree AV block
  - Fatigue, dizziness, and light-headedness are common and, with concomitant structural heart disease, heart failure, weakness, chest pain, confusion and syncope may occur
  - Associated with **profound bradycardia**
  - Can cause asystole leading to cardiac arrest and/or death

Etiology

- Degenerative changes (eg, fibrosis, calcification, or infiltration) are the most common cause of non-ischemic AV block.
- Idiopathic fibrosis or calcification of the AV conduction system, commonly seen in the elderly, can cause complete AV block.

Prognosis

- The prognosis in atrioventricular (AV) block is directly related to its degree and the patient's underlying medical problems. Those with advanced AV block who are not treated with permanent pacing remain at risk for syncope and sudden cardiac death, especially individuals with underlying structural heart disease.

In severe bradycardia to restore the rhythm of heart

Isoprenaline is a sympathomimetic that acts almost exclusively on **beta-adrenergic receptors.**

It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate

- Infusion rates may range from 0.5 to 10 micrograms/minute depending on the clinical condition of the patient
- 1 to 4 micrograms/minute may be adequate to correct bradycardia

Martindale 36th Edn, pg 1317

Uses

- For mild or transient episodes of heart block that do not require electric shock or pacemaker therapy. - for serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation)
- For use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, are available
- For brochospasm occurring during anaesthesia.
- As an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of hypovolaemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure and cariodgenic shock

https://www.healthdirect.gov.au/medicines/brand/amt,162803100016810 2/isoprenaline-cipla

Indications

- Treatment of permanent bradycardia due to atrio-ventricular block pending or in the case of contraindication of a pacemaker.
- Treatment of Adams-Stokes syndrome

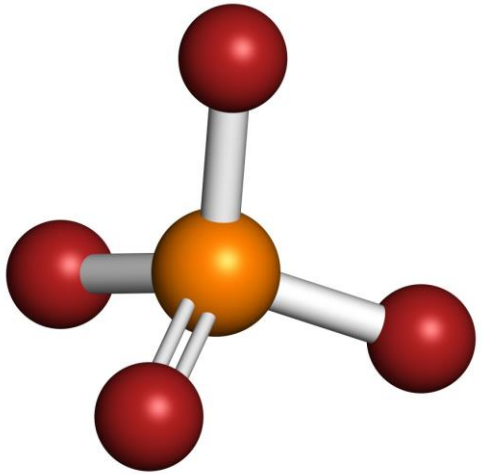
https://www.medicines.org.uk/emc/product/12511/smpc#gref

Potassium Phosphate

Phosphate

- Phosphate is an **essential electrolyte** in the human body as it constitutes about **1% of the total body weight.**

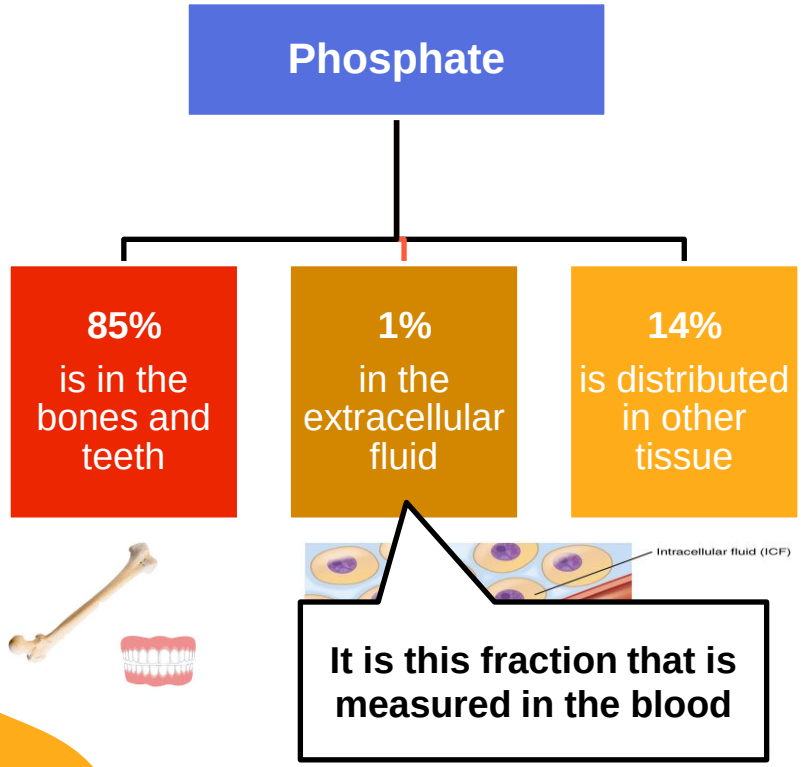
- Phosphate is **readily available in our diet** as it is present in almost all-natural foods. Important dietary sources of phosphate are milk, cereal grains, fish, poultry, eggs, meat, and peanuts.



Phosphate PO_4^{3-}
Tetrahedral Pyramid

Qadeer HA et al., StatPearls; Jan 2023; last accessed on 13th July 2023

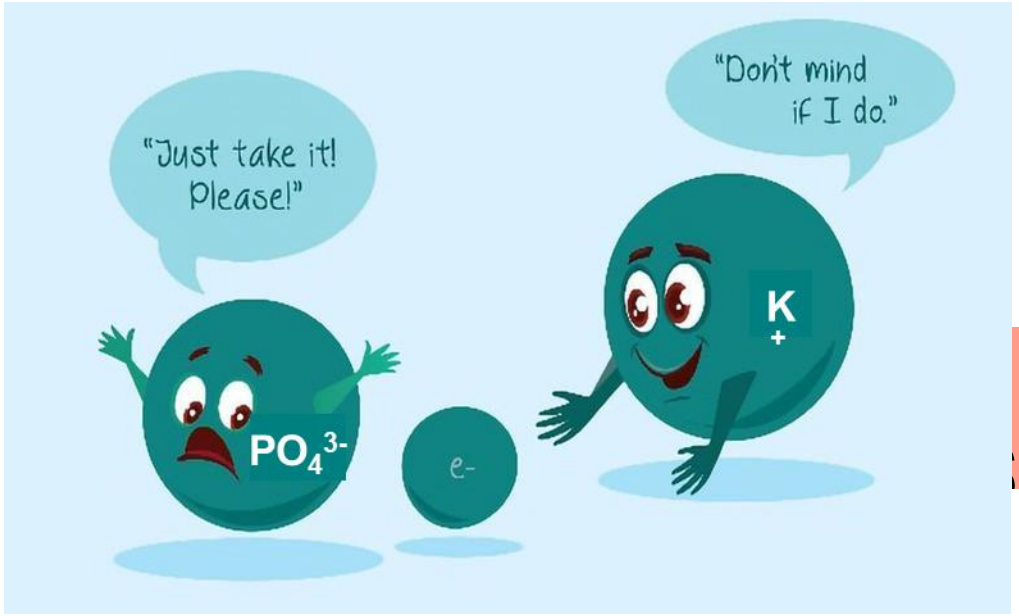
Phosphate Storage



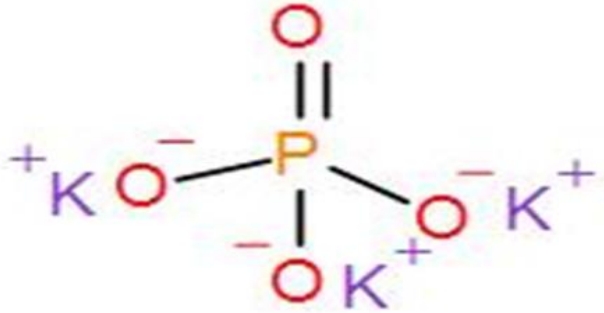
It is an important constituent of

- ✓ Cell Membranes
- ✓ Nucleic Acids
- ✓ High Energy Phosphate Esters (ATP)
- ✓ Intracellular Signaling Proteins

Qadeer HA et al., StatPearls; Jan 2023; last accessed on 13th July 2023



sium?



tripotassium phosphate

What is Hypophosphatemia?

Hypophosphatemia

For adults, **hypophosphatemia** is generally defined by **serum phosphate concentration below 2.5 mg/dl (0.8 millimolar)**

Parameters	Values
Mild	2-2.5 mg/dL, or 0.65-0.81 mmol/L
Moderate	1-2 mg/dL, or 0.32-0.65 mmol/L
Severe	< 1 mg/dL, or 0.32 mmol/L

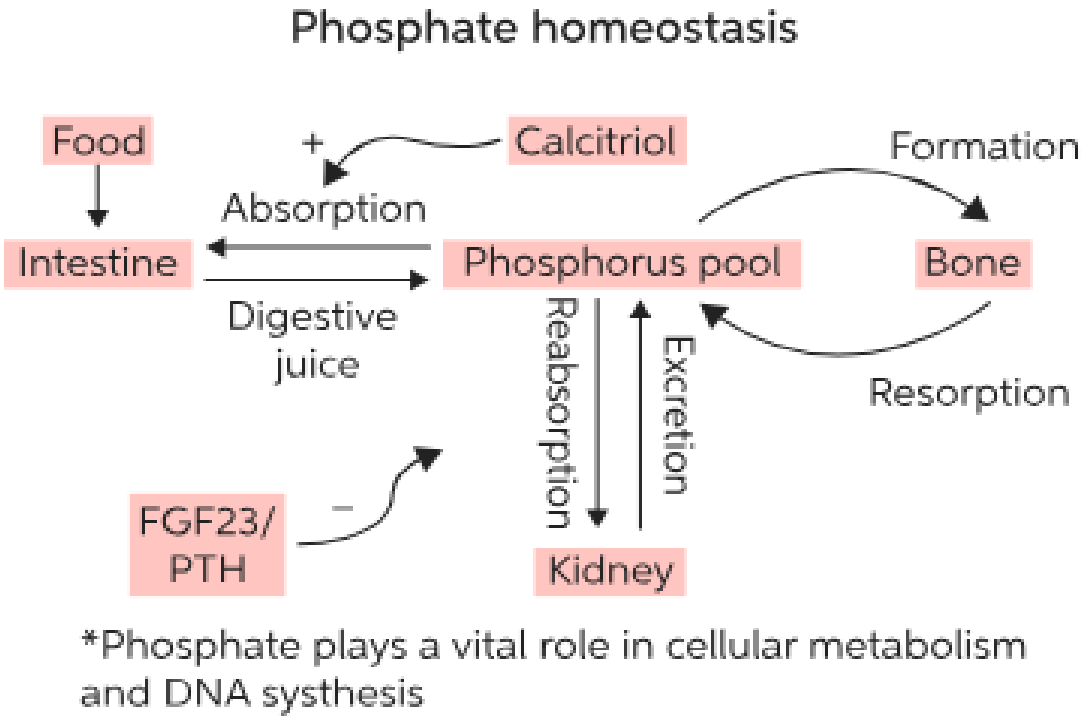
Mild to moderately severe hypophosphatemia is usually asymptomatic.

Major clinical sequelae occurs in severe hypophosphatemia.

Qadeer HA et al., StatPearls; Jan 2023; last accessed on 13th July 2023

Phosphorus Haemostatis

- Regulated by parathyroid, bone, and kidney, interacting with one another through feedback loops.
- PTH causes phosphate to be released from bone and inhibits renal reabsorption of phosphorus, resulting in phosphaturia.
- Vitamin D aids in intestinal reabsorption of phosphorus.



Prevalence of Hypophosphatemia

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prevalence of hypophosphatemia in the ICU – Results of an international one-day point prevalence survey

M.M. Berger [a, *], O. Appelberg [b], A. Reintam-Blaser [c], C. Ichai [d], O. Joannes-Boyau [e], M. Casaer [g], S.J. Schaller [f], J. Gunst [h], J. Starkopf [i], for the ESICM-MEN section [1]

- HypoP is present at least in 15.4% of ICU patients, and may occur at any time during the ICU stay.
- Half of the hypophosphatemic patients had a severe alteration.
- The prevalence number is likely to be an underestimation.

Berger MM, et al. Clinical Nutrition 40 (2021) 3615e3621

Pathophysiology

Hypophosphatemia is caused by:

1. Internal redistribution (Intracellular shift of phosphate from serum),
2. Decreased intestinal absorption
3. Increased urinary excretion
4. Removal by kidney replacement therapies

www.uptodate.com; Causes of Hypophosphatemia

Clinical manifestations

- Most patients with hypophosphatemia are asymptomatic.
- Occasionally, patients with mild hypophosphatemia may complain of weakness.

www.medscape.com; hypophosphatemia; last accessed on 18th July 2023

Clinical Consequences

Severe acute hypophosphatemia can have a variety of signs and symptoms

- Rhabdomyolysis (muscle weakness)
- Hypophosphatemic osteomalacia
- Hemolysis
- Leukocyte dysfunction
- Respiratory failure
- Impaired myocardial performance
- Diabetic ketoacidosis
- Perturbed central nervous system (muscular weakness, paresthesia, convulsions and coma)

Amanzadeh J, et al. Nature Clinical Practice Nephrology 2006; 2: 136–148

Clinical significance in ICU

Wang *et al. BMC Anesthesiology* (2019) 19:86
https://doi.org/10.1186/s12871-019-0746-2

BMC Anesthesiology

RESEARCH ARTICLE Open Access

Impact of hypophosphatemia on outcome of patients in intensive care unit: a retrospective cohort study

Lichun Wang, Chaoxing Xiao, Lei Chen, Xiaofei Zhang and Qiuye Kou*

Hypophosphatemia at admission is an independent risk factor for 28-day mortality in general ICU patients

Wang et al. BMC Anesthesiology (2019) 19:86

Association of hypophosphatemia with clinical outcomes in ICU

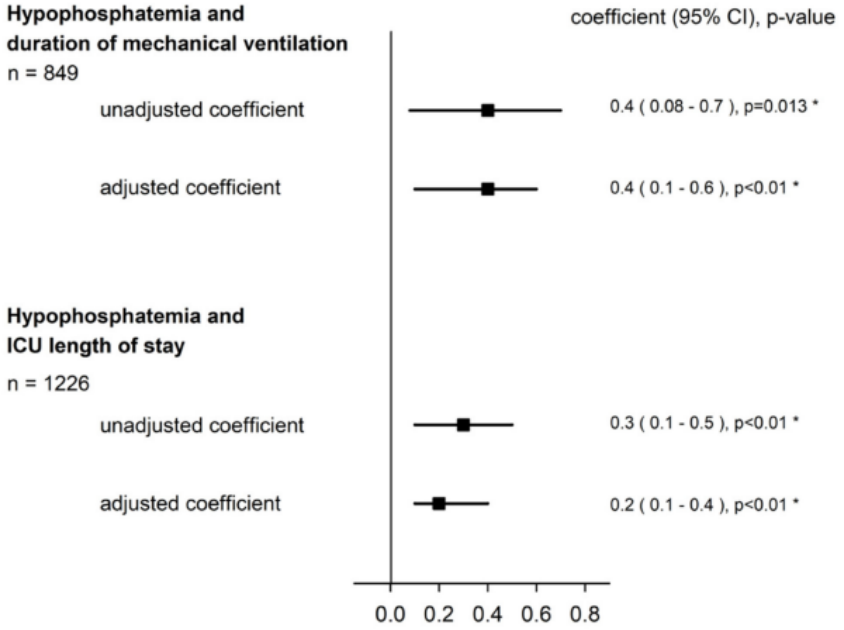
	Total	Control	Hypophosphatemia	*P*
28-day in ICU mortality (%)	284 (30.0%)	106 (24.0%)	178 (35.3%)	0.00
ICU LOS (days), median (IQR)	3.4 (1.7, 6.7)	1.7 (1.5, 3.4)	5.5 (2.8, 10.6)	0.00
Hospital LOS (days), median (IQR)	23.5 (13.6, 37.6)	20.6 (12.6,31.4)	27.1 (15.6, 27.1)	0.00
Proportion of MV (%)	526 (55.6%)	172 (38.9%)	354 (70.23%)	0.00
MV (days), median (IQR)	3.0 (1.0, 6.8)	1.2 (0.7,2.9)	4.4 (2.9, 9.0)	0.00
Proportion of RRT (%)	133 (14.1%)	39 (8.8%)	94 (18.7%)	0.00
Duration of RRT (h), median (IQR)	66 (35,141)	41 (22.0,59.0)	81.0 (45.3188.8)	0.03

ICU = Intensive Care Unit, *LOS* = length of stay, *IQR* = interquartile ranges; *MV* = mechanical ventilation, *IQR* = interquartile ranges, *CRRT* = continuous renal replacement therapy

Wang et al. BMC Anesthesiology (2019) 19:86

Hypophosphatemia and Duration of Mechanical Ventilation

- Significant association between hypoP and duration of mechanical ventilation
- hypoP at ICU admission multiplied the duration of mechanical ventilation by 1.5 days

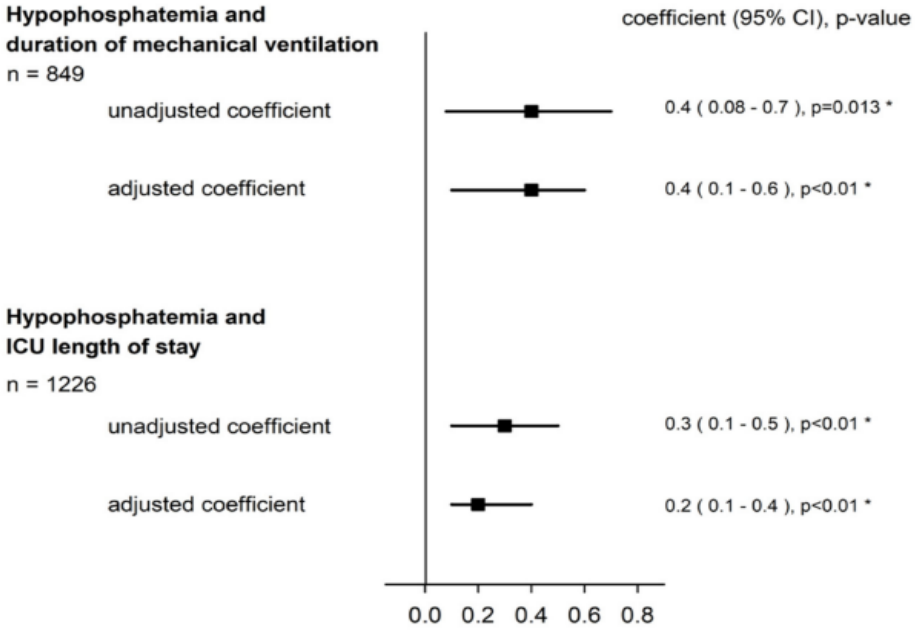


Hypophosphatemia, duration of mechanical ventilation, and ICU LOS in all ICU patients. Days of Mechanical Ventilation Regression coefficient

Wozniak H, et al. J. Clin. Med. 2022, 11, 581.

Hypophosphatemia and ICU Length of Stay

A significant association between hypoP at admission and ICU LOS was also observed hypoP at admission multiplied the ICU LOS by 1.2 days.



Hypophosphatemia, duration of mechanical ventilation, and ICU LOS in all ICU patients.

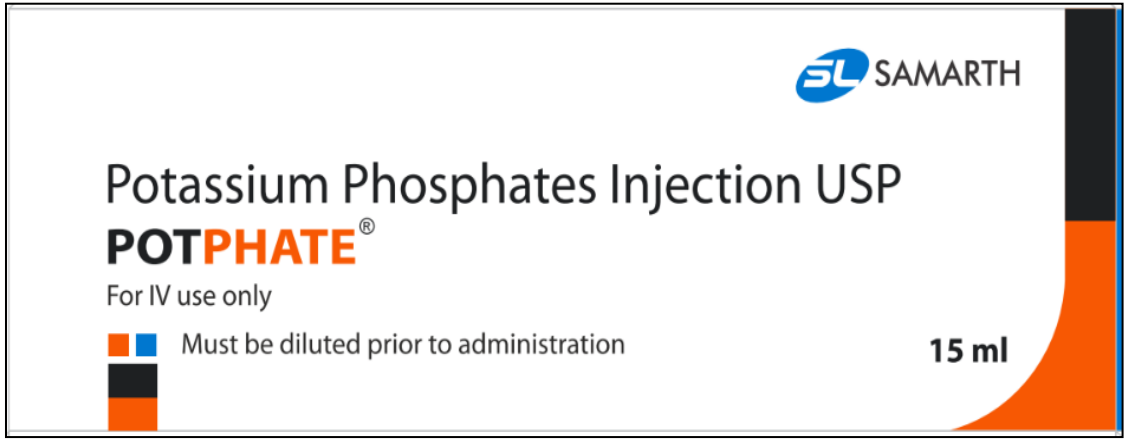
Wozniak H, et al. J. Clin. Med. 2022, 11, 581.

Conclusion

This study highlights the value of plasma phosphate levels measured on ICU admission as an **early indicator** of ICU length of stay and duration of mechanical ventilation.

Wozniak H, et al. J. Clin. Med. 2022, 11, 581.

Product Attributes



Composition:
Each ml contains:

Monobasic Potassium Phosphate (anhydrous) USP-NF	224 mg
Dibasic Potassium Phosphate USP (anhydrous)	236 mg
Water for Injections IP	q.s.

[Each ml provides 93 mg (3mM) of Phosphorus and 170 mg (4.4 mEq) of Potassium] 45 mM/15 ml Phosphorus & 66 mEq/15 ml Potassium. Total osmolar concentration is 7.4 mOsmol/ml.

Dosage: As directed by the Physician.

Storage: Store below 25°C. Protect from light.

Keep the medicine out of reach of children.

Once opened any unused portion is to be discarded.

Use only if solution is clear.

Caution: Not to be sold by retail without the prescription of a Registered Medical Practitioner.

Indication

- **In Intravenous Fluids to Correct Hypophosphatemia**

POTASSIUM PHOSPHATES INJECTION is indicated as a **source of phosphorus in intravenous fluids to correct hypophosphatemia** in adults and pediatric patients **12 years of age** and older when oral or enteral replacement is not possible, insufficient or contraindicated.

- **For Parenteral Nutrition**

POTASSIUM PHOSPHATES INJECTION is indicated as a **source of phosphorus for parenteral nutrition in adults weighing at least 45 kg** and pediatric patients **12 years of age** and older **weighing at least 40 kg** when oral or enteral nutrition is not possible, insufficient or contraindicated.

Limitations of Use Safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risk of aluminum toxicity.

Dosing Recommendation

POTASSIUM PHOSPHATES INJECTION is for intravenous infusion into a central or peripheral vein only after dilution

Using aseptic technique, withdraw the required dose from the vial and add to **100 mL to 250 mL of 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W).**

The **recommended maximum concentration** is:

- phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL) for peripheral administration
- phosphorus 18 mmol/100 mL (potassium 28.2 mEq/100mL) for central administration

Visually inspect the solution for particulate matter and discoloration before and after dilution and prior to administration. Do not administer unless solution is clear, and seal on the vial is intact.

Dosage for Administration in Intravenous Fluids to Correct Hypophosphatemia

INITIAL OR SINGLE DOSE

Recommended Initial or Single Dose of POTASSIUM PHOSPHATES INJECTION in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients 12 Years of Age and Older

Serum Phosphorus Concentration[a]	Phosphorus Dosage [b, c]	Corresponding Potassium Content
1.8 mg/dL to 2.4 mg/dL	0.16 mmol/kg to 0.31 mmol/kg	0.25 mEq/kg to 0.49 mEq/kg of potassium
1 mg/dL to 1.7 mg/dL	0.32 mmol/kg to 0.43 mmol/kg	0.5 mEq/kg to 0.68 mEq/kg of potassium
Less than 1 mg/dL	0.44 mmol/kg to 0.64 mmol/kg	0.69 mEq/kg to 1 mEq/kg of potassium

[a] Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults. Serum phosphorus concentrations may vary depending on the assay used and the laboratory reference range.

[b] Weight is in terms of actual body weight. Limited information is available regarding dosing of patients significantly above ideal body weight; consider using an adjusted body weight for these patients.

[c] up to a maximum of phosphorus 45 mmol (potassium 71 mEq) as a single dose.

Dosage for Administration in Parenteral Nutrition

Recommended Daily Dosage of POTASSIUM PHOSPHATES INJECTION for Parenteral Nutrition

Patient Population	Generally Recommended Phosphorus Daily Dosage (Potassium Content)	Maximum Phosphorus Dosage (Potassium Content) Based Upon Aluminum Conten
Adults weighing at least 45 kg	20 mmol/day to 40 mmol/day[b] (potassium 31 mEq/day to 62.7 mEq/day)	45 mmol/day (potassium 71 mEq/day)
Pediatric patients 12 years of age and older weighing at least 40 kg		40 mmol/day (potassium 62.7 mEq/day)

[b] In patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), start at the low end of the dosage range.

ADVERSE REACTIONS

Adverse Reactions Reported in Clinical Studies or Post-marketing Reports with Intravenous Potassium Phosphates

System Organ Class	Adverse Reactions
Metabolism and Nutrition Disorders	pulmonary embolism due to pulmonary vascular precipitates, hyperkalemia, hyperphosphatemia, hypocalcemia, hypovolemia, and osmotic diuresis
Cardiac Disorders	hypotension, arrhythmia, heart block, cardiac arrest, bradycardia, chest pain, ECG changes, and edema
Respiratory, Thoracic, and Mediastinal Disorders	dyspnea
Renal and Urinary Disorders	acute phosphate nephropathy (i.e., nephrocalcinosis with acute kidney injury), decreased urine output, and transition to chronic kidney disease
Gastrointestinal Disorders	diarrhea, stomach pain
Musculoskeletal and Connective Tissue Disorders	weakness
Nervous System Disorders	confusion, lethargy, paralysis, paresthesia

WARNINGS AND PRECAUTIONS

- Serious Cardiac Adverse Reactions with Undiluted, Bolus or Rapid Intravenous Administration
- Pulmonary Embolism due to Pulmonary Vascular Precipitates
- Hyperkalemia
- Hyperphosphatemia and Hypocalcemia
- Aluminum Toxicity
- Hypomagnesemia
- Vein Damage and Thrombosis

Monitor serum phosphorus, potassium, calcium and magnesium concentrations during treatment.

SPECIAL POPULATION

Pregnancy	Parenteral supplementation with potassium phosphates **should be considered if a pregnant woman's requirements cannot be fulfilled by oral or enteral intake.**
Lactation	The **developmental and health benefits of breastfeeding** should be considered along with the mother's clinical need for POTASSIUM PHOSPHATES INJECTION and any **potential adverse effects** on the breastfed infant from POTASSIUM PHOSPHATES INJECTION or from the underlying maternal condition.
Paediatric Use	Safety and effectiveness of POTASSIUM PHOSPHATES INJECTION have been established in: • **pediatric patients 12 years and older** as a source of phosphorus in **intravenous fluids to correct hypophosphatemia** when oral or enteral replacement is not possible, insufficient, or contraindicated. • **pediatric patients 12 years and older weighing at least 40 kg** as a source of phosphorus for **parenteral nutrition** when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Contd….

<table>
<tr><td>Geriatric Use</td><td><u>Start at the low end of the dosing range</u> because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy</td></tr>
<tr><td>Renal impairment</td><td>Potassium and phosphorus are known to be substantially <u>excreted by the kidney</u> and the <u>risk of adverse reactions to POTASSIUM PHOSPAHTES INJECTION may be greater</u> in patients with impaired renal function.
<table>
<tr><td><u>Severe renal impairment</u> (eGFR less than 30 mL/min/1.73 m^2) or end stage renal disease.</td><td><u>Contraindicated</u> due to the risk of hyperkalemia</td></tr>
<tr><td><u>Moderate renal impairment</u> (eGFR ≥ 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2)</td><td><u>Start at the low end of the dosage range</u> and monitor serum potassium, phosphorus, calcium, and magnesium concentrations</td></tr>
</table></td></tr>
</table>

CONTRAINDICATIONS

POTASSIUM PHOSPHATES INJECTION is contraindicated in patients with:

- hyperkalemia
- hyperphosphatemia
- hypercalcemia or significant hypocalcemia
- severe renal impairment (eGFR less than 30 mL/min/1.73m^2) and end stage renal disease

Clinical Evidences

Intensive Care Med (2003) 29:1273–1278
DOI 10.1007/s00134-003-1872-2

ORIGINAL

Thierry Charron
Francis Bernard
Yoanna Skrobik
Nathalie Simoneau
Nadine Gagnon
Martine Leblanc

Intravenous phosphate in the intensive care unit: More aggressive repletion regimens for moderate and severe hypophosphatemia

Aim: To evaluate efficacy and safety of aggressive correction of hypophosphatemia with intravenous potassium phosphate in the ICU.

- Patients with moderate hypophosphatemia (<0.65 and >0.40 mmol/l; *n*=37) were randomized into two groups:

✓ Group 1 received 30 mmol potassium phosphate intravenously in 50 ml saline over 2 h,

✓ Group 2 received 30 mmol potassium phosphate in 100 ml saline over 4 h.

- Patients with severe hypophosphatemia (<0.40 mmol/l; *n*=10) were also randomized into two groups:

✓ Group 3 received 45 mmol potassium phosphate intravenously in 100 ml saline over 3 h,

✓ Group 4 received 45 mmol potassium phosphate in 100 ml saline over 6h.

- Electrolytes, blood gas, renal function were monitored until day 3; urine was collected during and until 6 h after infusions.

Results

Electrolyte concentrations (mmol/l) during potassium phosphate infusion in the four study groups

	0 h	1 h	2 h	3 h	4 h	5 h	6 h	24 h[d]	48 h	72 h
Phosphate[a]										
Group 1	0.58±0.13	0.9±0.26	1.28±0.33[e]	–	–	–	–	0.86±0.22	0.93±0.28	1.19±0.45
Group 2	0.56±0.12	0.76±0.17	0.97±0.19*	1.09±0.25	1.20±0.32[e]	–	–	0.89±0.24	0.80±0.22	0.95±0.31
Group 3	0.38±0.03	0.79±0.49	1.27±0.39	1.32±0.32[e]	–	–	–	0.83±0.24	0.79±0.27	0.91±0.25
Group 4	0.31±0.10	0.44±0.27	0.61±0.27**	0.77±0.34**	0.97±0.39	1.07±0.35	1.07±0.2[e]	0.61±0.22	0.72±0.31	0.86±0.31

- Intravenous potassium phosphate administered rapidly (30 mmol in 2 or 4 h or 45 mmol in 3 or 6 h) to ICU patients with diverse pathological conditions and no significant renal insufficiency (creatinine <200 µmol/l) is a safe and effective treatment for correcting moderate and severe hypophosphatemia.
- Protocols used in this study have a 98% efficacy in correcting hypophosphatemia by the end of infusion.

Conclusion

In summary, ICU patients are prone to hypophosphatemia which can lead to several physiological alterations in cell function. These potential deleterious effects are reversed by phosphate supplementation. Rapid correction of phosphate deficit, as demonstrated here, appears safe. To prevent additional insult to tissues from phosphate deficit and because phosphate infusion is incompatible with many other medications we suggest infusing phosphate in the following manner: 30 mmol potassium phosphate over 2 h or 45 mmol over 3 h in patients with a baseline serum potassium below 4.0 mmol/l and creatinine below 200 µmol/l. Slower protocols (i.e., 30 mmol potassium phosphate over 4 h or 45 mmol over 6 h) or sodium phosphate (which is more expensive) are as efficacious and should be favored if kalemia is a concern.

Thank You

Metabolic Acidosis

Understanding Acid-Base Balance

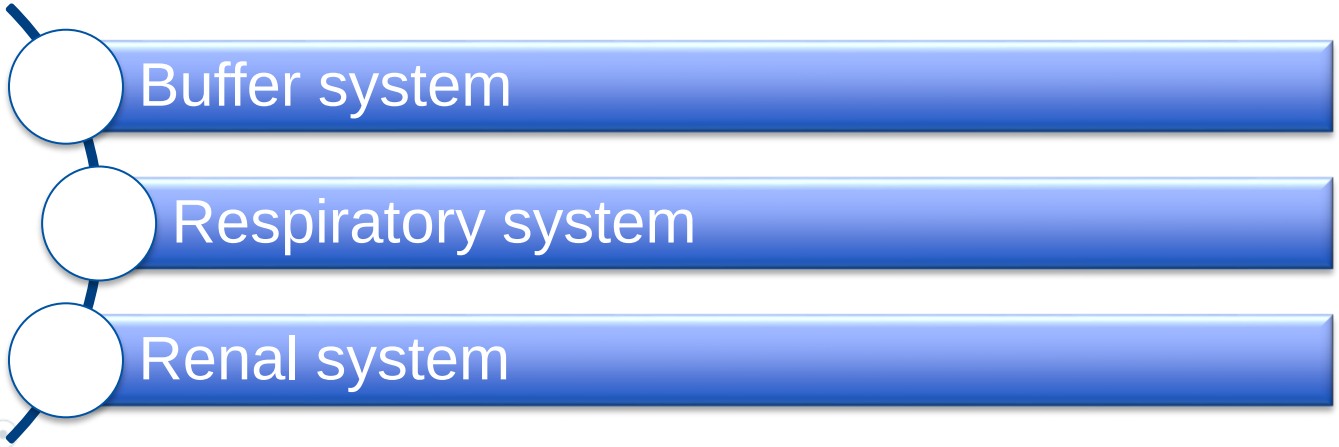
- Every chemical reaction that occurs in the human body is regulated by the hydrogen ion (H+) concentration in the surrounding tissue
- Regulation of hydrogen ions, which we measure as “pH,” is what acid-base balance refers to

pH	Concentration of H+ ions	Patient’s condition
7.35-7.45	Normal	Normal
Below 7.35	Increased	Acidosis
Above 7.45	Decreased	Alkalosis

Proper balance between the acids and bases (i.e. the pH) in the ECF is crucial for the normal physiology of the body—and for cellular metabolism

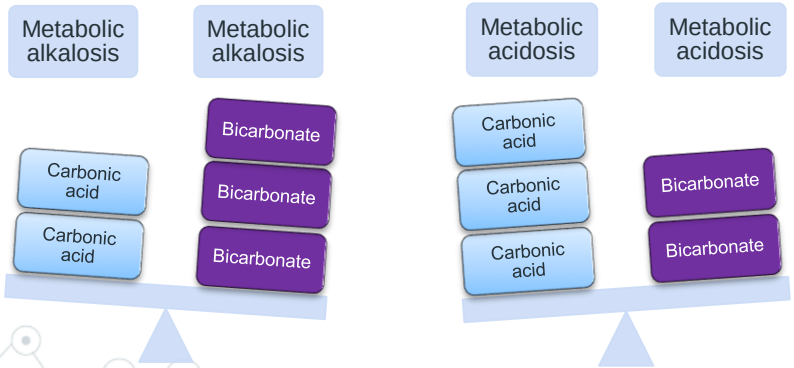
How is excess of acid produced

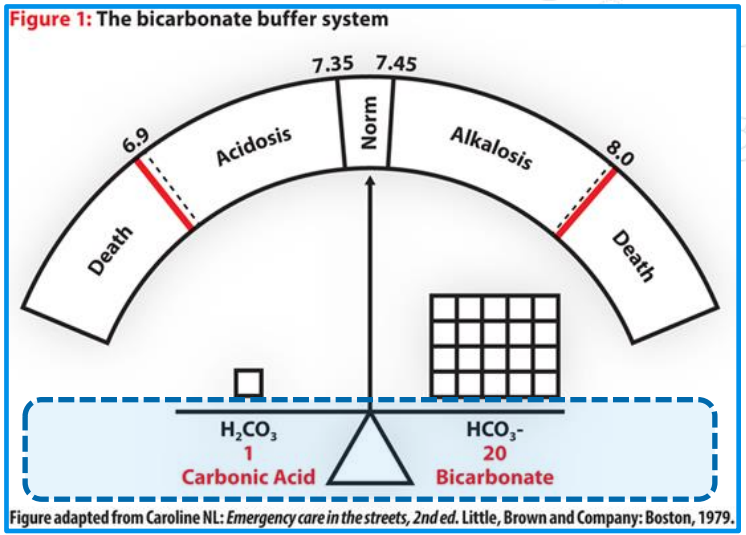
- Usually produced during the normal process of metabolism
- Three defense mechanisms handle excess acid



Management of excess acid: Buffer system

- Occurs in a fraction of a second
- Buffer system soaks up excessive hydrogen ions and releases them when there's a deficient concentration.

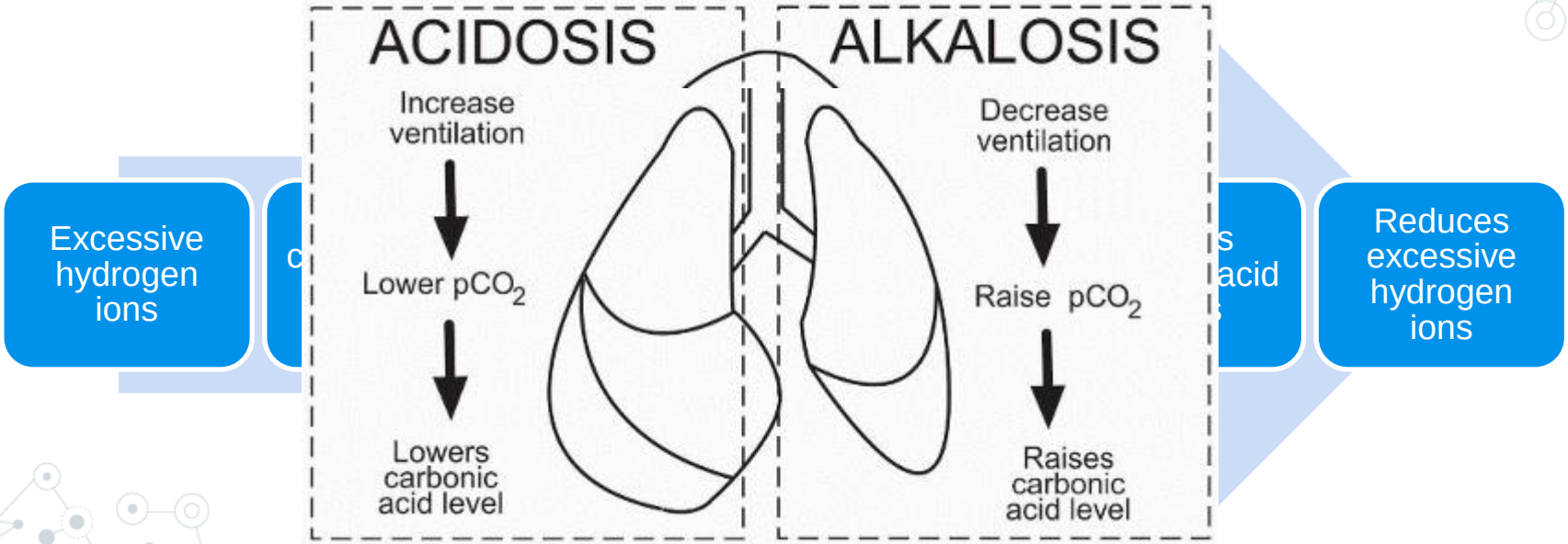




These chemical changes occur via the carbonate system, which consists of a mixture of carbonic acid and bicarbonate in a normal ratio of 1:20

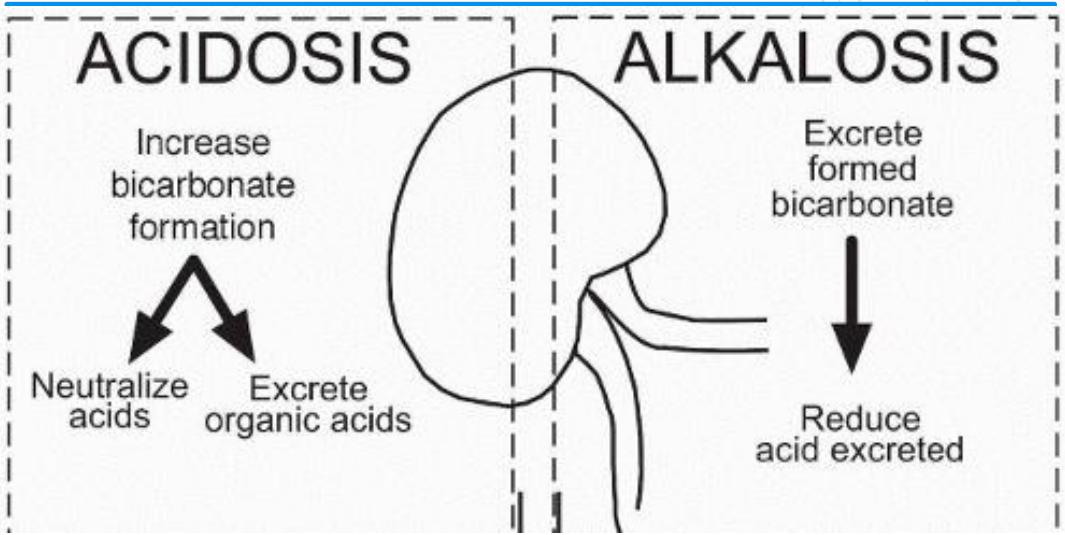
Management of excess acid: Respiratory system

- Slower than the buffer system
- Plays a key role in acid-base regulation



Management of excess acid: Renal system

- Much slower
- Takes hours to days
- More important in the long-term maintenance of acid-base balance



Development of metabolic acidosis

- Increased production of nonvolatile acids (not excreted by the lungs)
- Increased loss of bicarbonate
- Decreased renal excretion of acid

Metabolic acidosis

- Electrolyte disorder characterized by an imbalance in the body's acid-base balance
- ***Serum bicarbonate of <22 mEq/L***

Etiology

- GI loss of HCO_3^- (Diarrhea)
- Enterocutaneous fistula (eg, pancreatic) - Enteric diversion of urine (eg, ileal loop bladder), pancreas transplantation with bladder drainage
- Renal loss of HCO_3^- - Proximal RTA (type 2), carbonic anhydrase inhibitor therapy
- Failure of renal H^+ secretion - Distal RTA (type 1), hyperkalemic RTA (type 4), kidney failure
- Acid infusion - Ammonium chloride, hyperalimentation
- Other - Rapid volume expansion with normal saline

RTA: Renal tubular acidosis: Occurs when bicarbonate is not properly reabsorbed by the kidney's filtering system.

Etiology

- Lactic acidosis
- Ketoacidosis (Starvation, T1DM)
- Advanced renal failure
- Salicylate overdose
- Methanol poisoning
- Ethylene glycol poisoning

Prognosis

- Morbidity and mortality in metabolic acidosis are primarily related to the underlying condition.

Presentation

- Diarrhea - Gastrointestinal (GI) losses of HCO 3 -
- History of diabetes mellitus, alcoholism, or prolonged starvation - Accumulation of ketoacids
- Polyuria, increased thirst, epigastric pain, vomiting - Diabetic ketoacidosis (DKA)
- Nocturia, polyuria, pruritus, and anorexia - Kidney failure [14]
- Ingestion of drugs or toxins - Salicylates, acetazolamide, cyclosporine, ethylene glycol, methanol, metformin, topiramate
- Visual symptoms, including dimming, photophobia, scotomata - Methanol ingestion
- Renal stones - Renal tubular acidosis (RTA) or chronic diarrhea
- Tinnitus, blurred vision, and vertigo - Salicylate overdose

Treatment

- Treatment of acute metabolic acidosis with alkali therapy is usually indicated to raise and maintain the plasma pH to greater than 7.20

Indications

- **Metabolic Acidosis:** Severe renal disease, uncontrolled diabetes, shock, severe dehydration, extracorporeal circulation, cardiac arrest, severe lactic acidosis
- **Drug Intoxications:** Barbiturates (to dissociate barbiturate-protein complex), salicylates, methyl alcohol, hemolytic reactions (to alkalinize urine and reduce nephrotoxicity)
- **Severe Diarrhea:** Loss of bicarbonate

Dosage

- **Cardiac Arrest:**
- Initial Dose: 1-2 vials (44.6 to 100 mEq) IV
- Continue: 50 mL (44.6 to 50 mEq) every 5-10 minutes if needed, guided by pH and blood gas levels
- Caution: Rapid infusion may raise plasma sodium levels; however, the risk from acidosis outweighs hypernatremia
- **Less Urgent Metabolic Acidosis:**
- Dosage: 2-5 mEq/kg body weight over 4-8 hours
- Monitor: Blood gases, plasma osmolarity, lactate, hemodynamics, and cardiac rhythm
- Adjust: Based on clinical response; reduce dose or frequency if symptoms improve

Special population

Pregnancy:

- Use only if clearly necessary

Pediatric:

- Rapid injection (10 mL/min) in children under 2 may cause hypernatremia, reduced cerebrospinal fluid pressure, and possible intracranial hemorrhage
- Limit dosage to 8 mEq/kg/day; prefer 4.2% solution for slow administration
- In emergencies, weigh the risks of rapid infusion against acidosis fatality

Geriatric:

- Insufficient data on elderly patients
- Start with a low dose, considering decreased organ function and other health factors

Adverse reactions

Risks of Aggressive Sodium Bicarbonate Therapy:

- Can cause metabolic alkalosis (symptoms: muscular twitching, irritability, tetany)
- May lead to hypernatremia

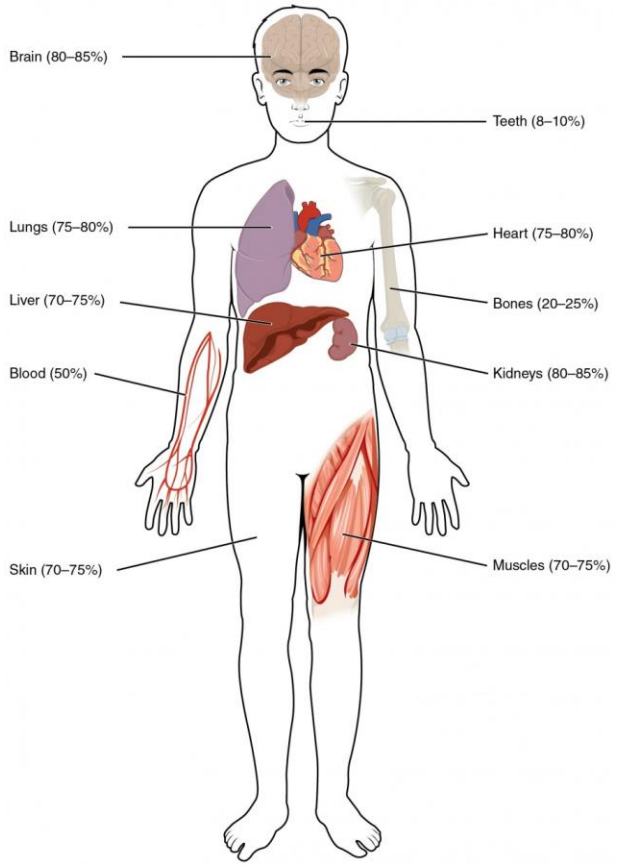
Extravasation Risks:

- Hypertonic sodium bicarbonate can cause chemical cellulitis, tissue necrosis, ulceration, or sloughing at the infusion site
- Treatment: Elevate the affected area, apply warmth, and consider local injection of lidocaine or hyaluronidase to reduce tissue damage

Hypokalemia

Body Fluids and Fluid Compartments

- Human beings are mostly water, ranging from about 75% of body mass in infants to about 50–60 percent in adult men and women, to as low as 45 percent in old age.
- Brain and kidneys have the highest proportions of water, (80–85 percent of their masses).
- Teeth have the lowest proportion of water, (8–10%).



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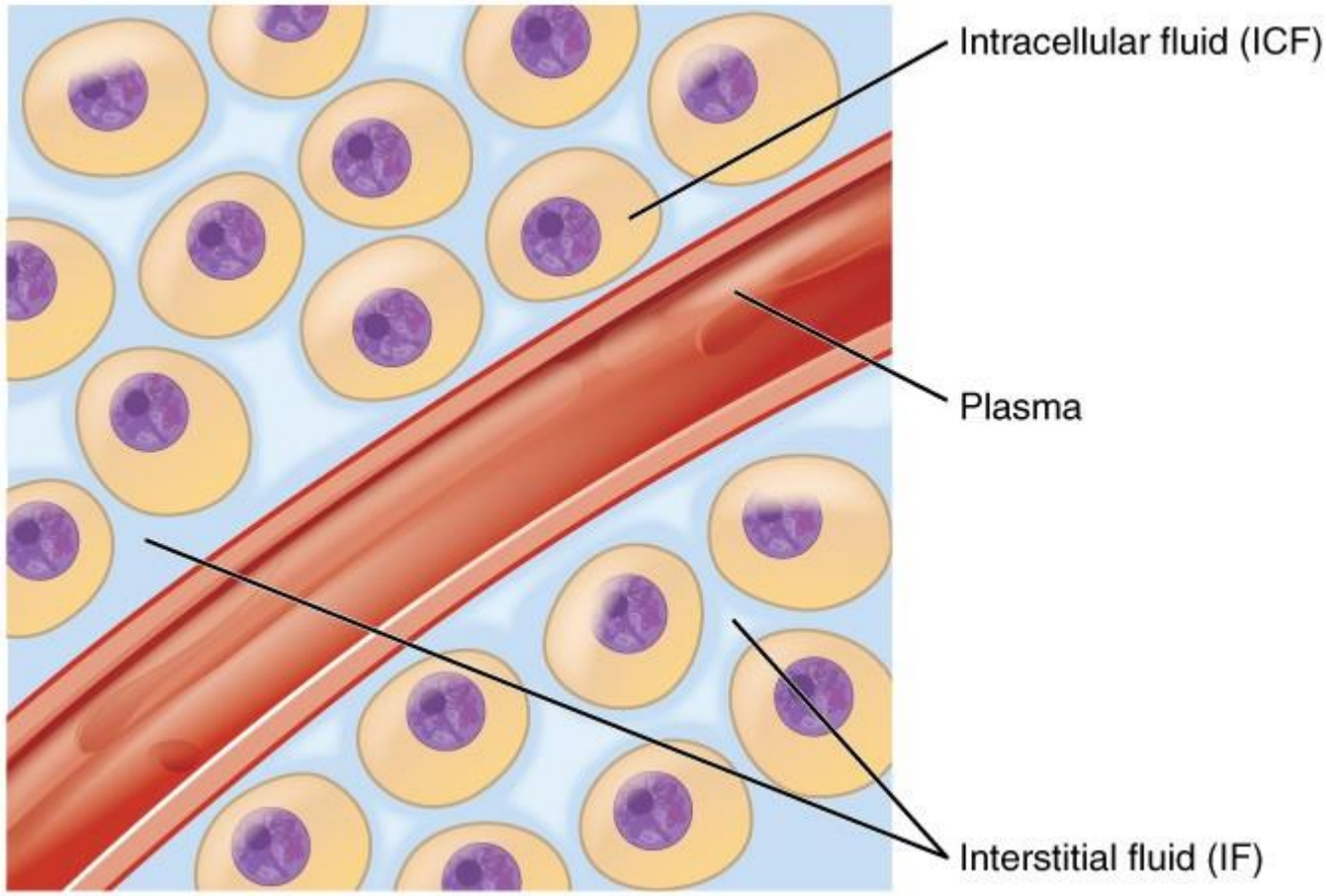
Fluid Compartments

- Intracellular fluid (ICF)
  - Includes all fluid enclosed in cells by their plasma membranes.
  - 60% of the total water (25 liters)

- Extracellular fluid (ECF)
  - Surrounds all cells in the body.
  - Has two primary constituents: the fluid component of the blood (called plasma) and the interstitial fluid (IF) that surrounds all cells not in the blood.
  - 1/3rd of the body's water content
  - 20% of the ECF is found in plasma



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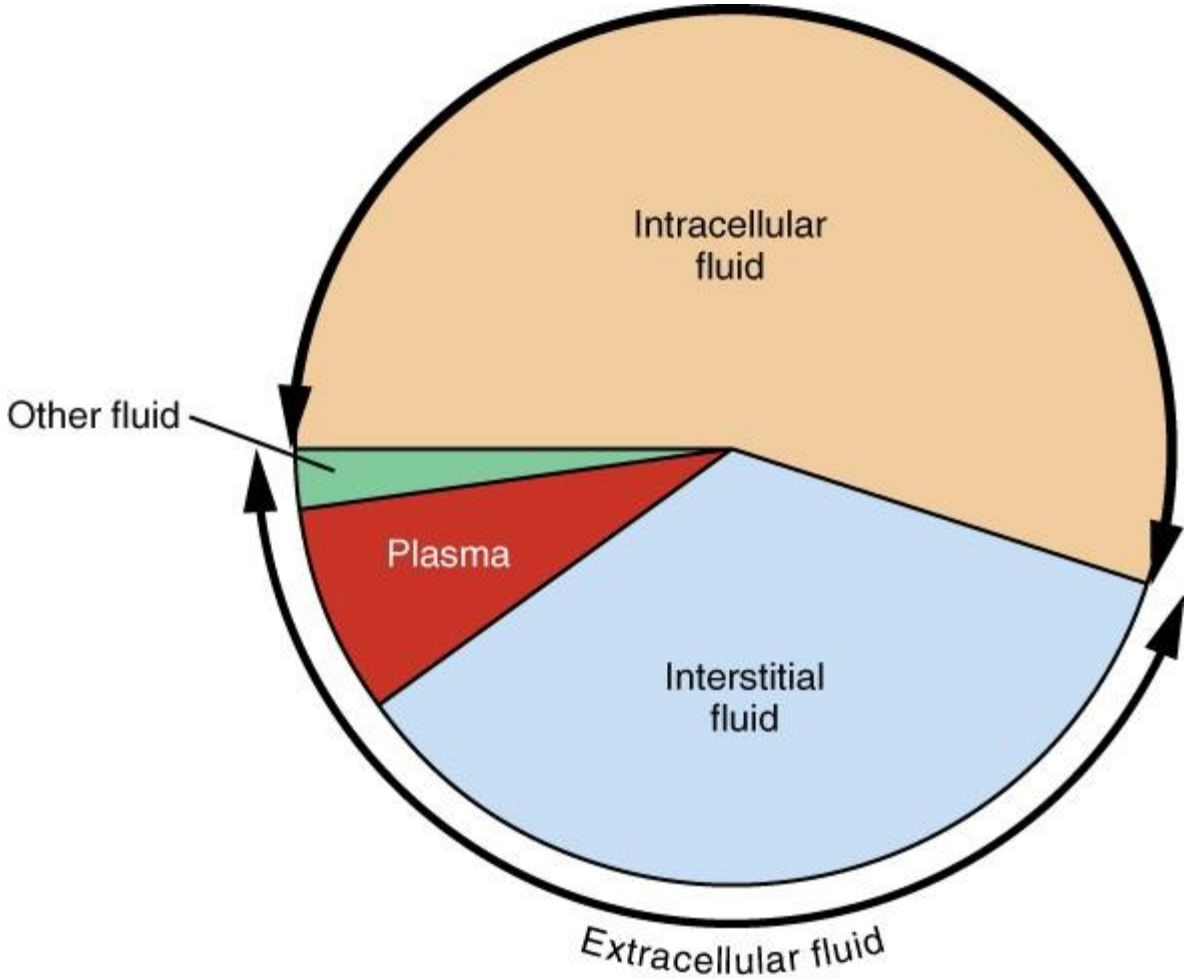
Fluid Compartments (Cont..)

- Most of the water in the body is intracellular fluid.
- The second largest volume is the interstitial fluid, which surrounds cells that are not blood cells.



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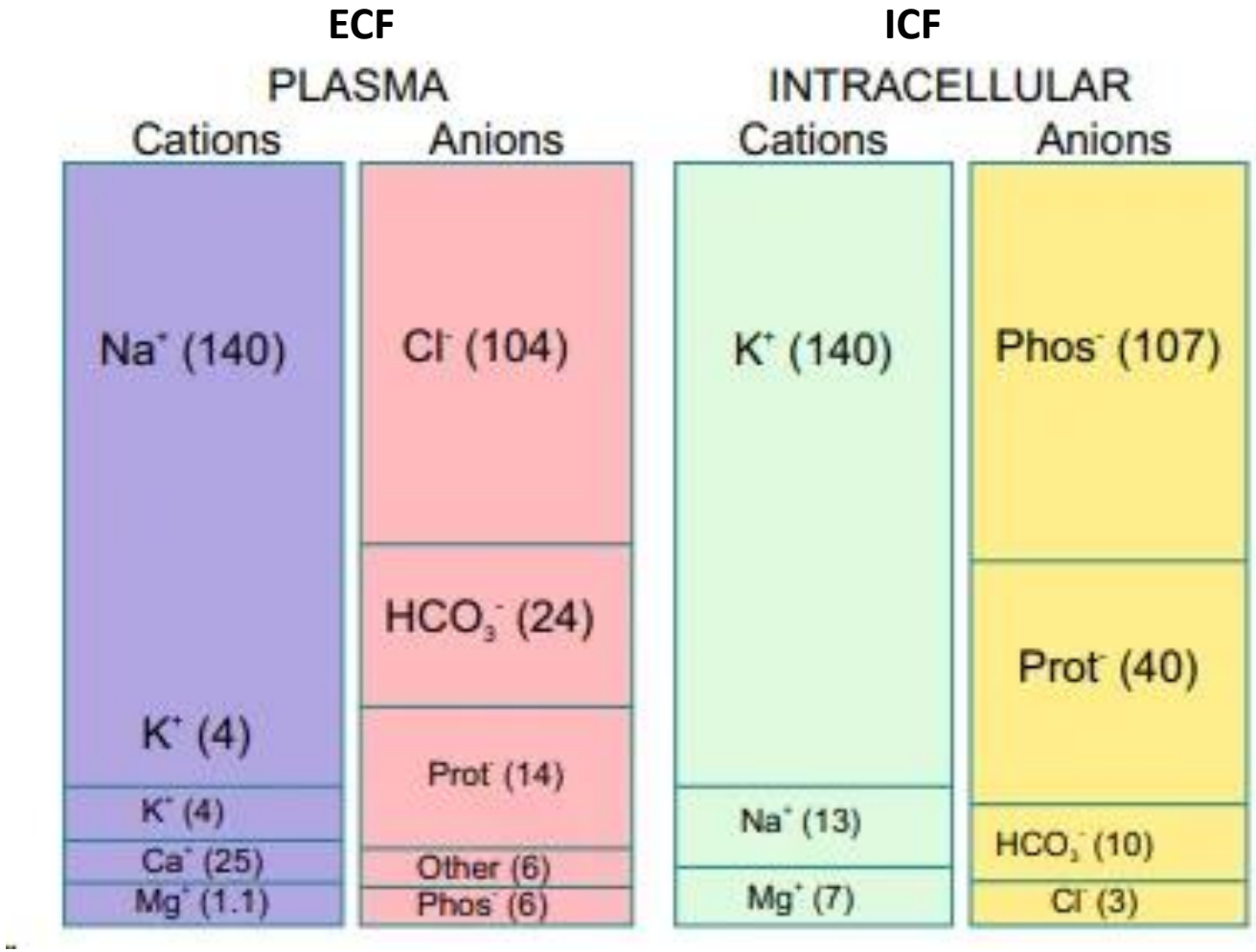
Osmotic equilibrium

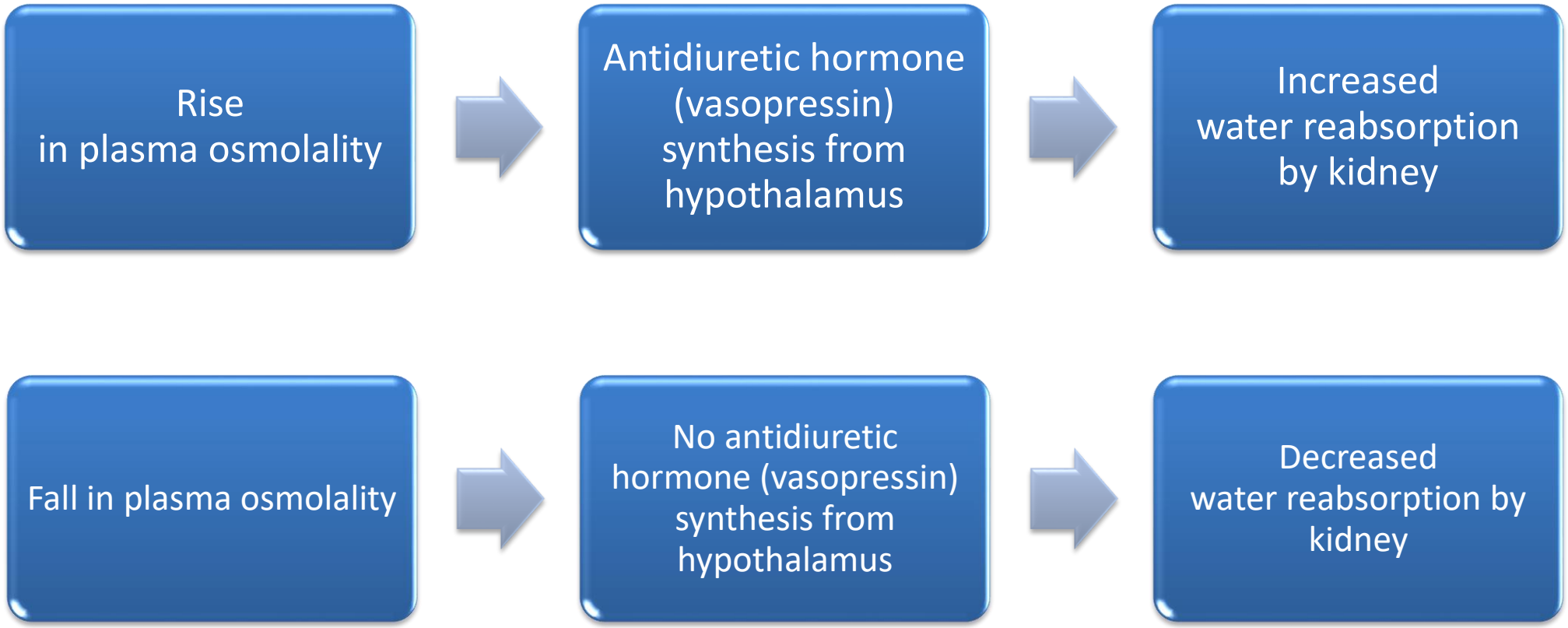
- ECF and ICF stay in osmotic equilibrium, which means ECF osmolality usually in physiological conditions equals the ICF osmolality

- **Osmolality:** Concentration of dissolved particles

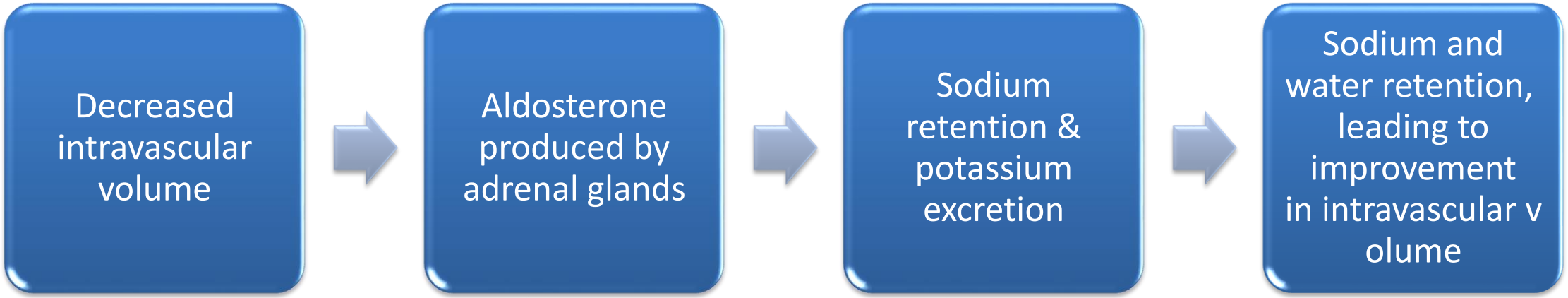


ADH and regulation of plasma osmolality

- Hypothalamic system regulates plasma osmolality. ADH causes reabsorption of water



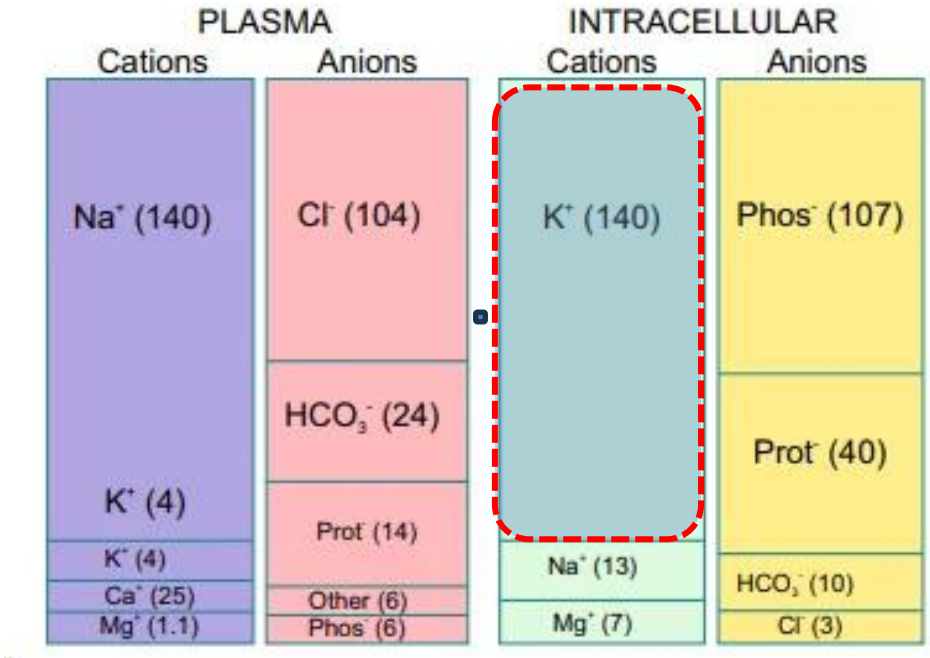
Aldosterone and Control Of Intravascular Volume



- Aldosterone is a hormone that increases blood volume and blood pressure by causing kidney reabsorption of water and sodium. It's important to note that ADH causes reabsorption of just water, while aldosterone causes reabsorption of water as well as sodium. In addition, aldosterone causes renal excretion of potassium.

Potassium

- Potassium is the most abundant intracellular cation (positively charged ions), is essential for the life of an organism.
- Potassium homeostasis is integral to normal cellular function, particularly of nerve and muscle cells, and is tightly regulated by specific ion-exchange pumps, primarily by cellular, membrane-bound, sodium-potassium adenosine triphosphatase (ATPase) pumps



Potassium homeostasis

- Gastrointestinal absorption results in daily excess intake of approximately 1 mEq/kg/day (60-100 mEq) of potassium. Of this excess, 90% is excreted through the kidneys, and 10% is excreted through the gut.
- Potassium homeostasis is maintained predominantly through the regulation of renal excretion; the adrenal gland and pancreas also play significant roles.

Potassium homeostasis

- Potassium excretion is increased by the following factors
  - Aldosterone
  - High sodium delivery to the collecting duct (eg, diuretics)
  - High urine flow (eg, osmotic diuresis)
  - High serum potassium levels
  - Delivery of negatively charged ions to the collecting duct (eg, bicarbonate)

- Potassium excretion is decreased by the following factors
  - Absolute aldosterone deficiency (Primary adrenal insufficiency)
  - Low sodium delivery to the collecting duct
  - Low urine flow
  - Low serum potassium levels
  - Renal failure

Hypokalemia

- Hypokalemia is generally defined as a serum potassium level of less than 3.5 mEq/L (3.5 mmol/L).
- Hypokalemia is a potentially life-threatening imbalance that may be iatrogenically induced

Pathogenic mechanisms of hypokalemia

- Increased excretion (Most common)
- Deficient intake
- A shift from the extracellular to the intracellular space

- Most common mechanisms leading to increased renal potassium losses
  - Enhanced sodium delivery to the collecting duct, as with diuretics
  - Mineralocorticoid excess, as with primary or secondary hyperaldosteronism
  - Increased urine flow, as with an osmotic diuresis
  - Gastrointestinal losses, from diarrhea, vomiting, or nasogastric suctioning, also are common causes

Complications of hypokalemia

- Cardiovascular complications
  - Most important harbingers of significant morbidity or mortality
  - Atrial and ventricular arrhythmias (ventricular tachycardia/fibrillation occur even with moderate hypokalemia)
- Muscular complications
  - Muscle weakness, depression of the deep-tendon reflexes, and even flaccid paralysis.
  - Rhabdomyolysis in severe hypokalemia
- Renal complications
  - Nephrogenic diabetes insipidus
- Gastrointestinal complications
  - decreases gut motility, which can lead to or exacerbate an ileus.
  - contributory factor in the development of hepatic encephalopathy

Epidemiology

- Fewer than 1% of people who are not taking medication have a serum potassium level lower than 3.5 mEq/L
- Up to 21% of hospitalized patients have serum potassium levels lower than 3.5 mEq/L, with 5% of patients exhibiting potassium levels lower than 3 mEq/L.
- Among elderly patients, 5% demonstrate potassium levels lower than 3 mEq/L.
- Of patients taking non–potassium-sparing diuretics, 20-50% develop hypokalemia

Epidemiology (Cont..)

- Risk of hypokalemia in patients taking diuretics is enhanced by concomitant illness, such as heart failure or nephrotic syndrome.

- Other factors associated with a high incidence of hypokalemia include the following:
  - Eating disorders (incidence of 4.6-19.7% in an outpatient setting
  - AIDS (23.1% of hospitalized patients)
  - Alcoholism (incidence reportedly as high as 12.6% in the inpatient setting, likely from a hypomagnesemia-induced decrease in tubular reabsorption of potassium
  - Bariatric surgery
  - Diabetes mellitus

Prognosis

- Depends entirely on the condition’s underlying cause.
- Patient with an acute episode of hypokalemia resulting from diarrhea has an excellent prognosis.
- Hypokalemia due to a congenital disorder such as Bartter syndrome has a poor to nonexistent potential for resolution

Signs and symptoms

- Symptoms are nonspecific and predominantly are related to ***muscular or cardiac function***
- Weakness and fatigue are the most common complaints.
- Muscular weakness
  - Manifest as dyspnea, constipation or abdominal distention, exercise intolerance
  - Rarely, muscle weakness progresses to frank paralysis.
  - Muscle cramps and pain can occur with rhabdomyolysis
- Worsening diabetes control or polyuria
- Palpitations
- Psychological symptoms (eg, psychosis, delirium, hallucinations, depression)

Treatment

- Reduction of potassium losses
- Replenishment of potassium stores
- Evaluation for potential toxicities
- Determination of the cause to prevent future episodes, if possible

Medications

- Decreasing Potassium Losses
  - Discontinue diuretics/laxatives
  - Use potassium-sparing diuretics if diuretic therapy is required (eg, severe heart failure)
  - Treat diarrhea or vomiting
  - Administer H2 blockers to patients receiving nasogastric suction
  - Control hyperglycemia if glycosuria is present

- Replenishment of Potassium
  - Oral potassium for mild or moderate hypokalemia (potassium level of 2.5-3.5 mEq/L)
  - Intravenous potassium if the potassium level is less than 2.5 mEq/L

Indication

- Indicated in the treatment of potassium deficiency states when oral replacement is not feasible

Contraindications

- Diseases where high potassium levels may be encountered, and in patients with hyperkalemia, renal failure and in conditions in which potassium retention is present

Adverse reactions

- Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, and hyperkalemia

- The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest

Dosage and administration

Dosage and administration of potassium depend on the patient's condition

For serum potassium levels above 2.5 mEq/L, potassium can be given at up to 10 mEq/hour, with a maximum of 200 mEq per 24 hours

For urgent cases with levels below 2.0 mEq/L and severe symptoms, potassium chloride can be infused cautiously at up to 40 mEq/hour, with a maximum of 400 mEq per 24 hours, and continuous cardiac monitoring is required

In critical conditions, potassium chloride should be administered in saline instead of dextrose, which can lower potassium levels

1. Introduction to pharmacology

2. Human anatomy and physiology

Introduction

Pharmacology

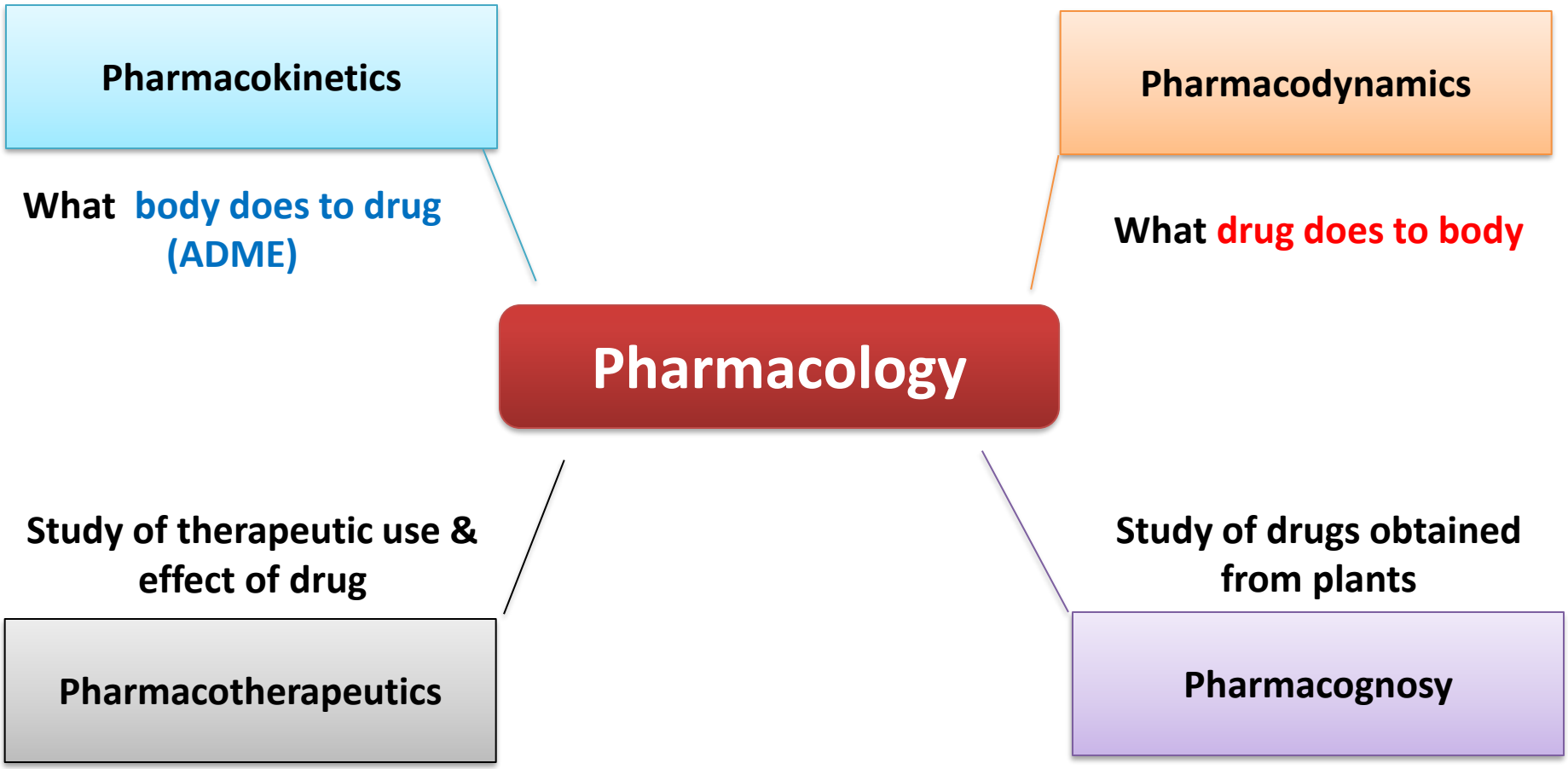
It is the science of drugs

Study of drugs and its action on the living organisms

Drug

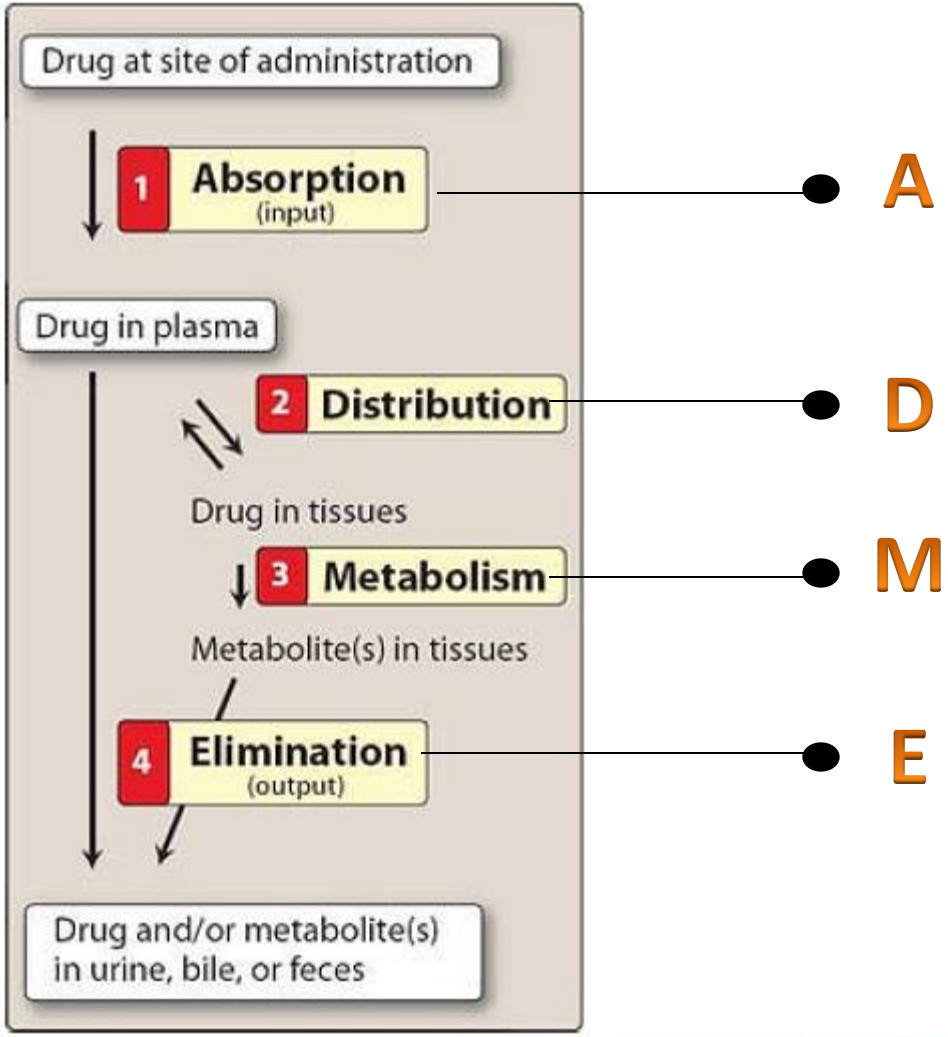
It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, or treatment of a disease

Introduction



Pharmacokinetics

"What body does to the drug"



Absorption

- Transfer of drug from site of administration to the blood

Distribution

- Transport of drug molecules by blood to different organs and tissues

Factors affecting Distribution

a) **Lipid Solubility** - More lipid soluble drug is distributed fast

b) **Blood supply to the organs**

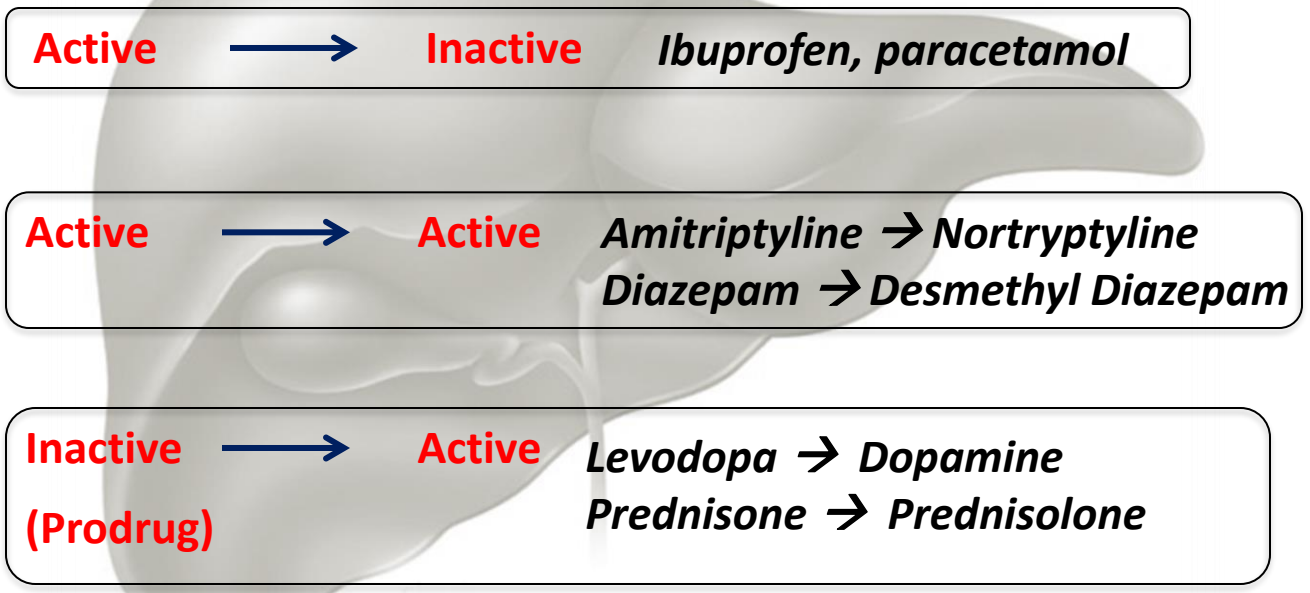
c) **Protein binding** – Drug molecules in blood are bound to proteins i.e. albumin & glycoprotein

Importance of Protein Binding

- Only free drug molecules can get distributed to tissues
- High degree of protein binding generally makes the drug long acting because bound fraction is not available for metabolism or excretion

Metabolism (Biotransformation)

- Breakdown of drug molecule into metabolites
- Main organ of metabolism is **LIVER,** Others: Kidney, intestine, lungs
- Metabolized by enzyme group; mainly Cytochrome p450 enzyme



Excretion

- Excretion is the removal of absorbed drug from body

- **Organs of excretion -**
  - ✓ Kidney → Urine
  - ✓ GIT → Feces
  - ✓ Skin → Sweat
  - ✓ Breast milk

Cmax, Tmax, $T_{1/2}$

Cmax

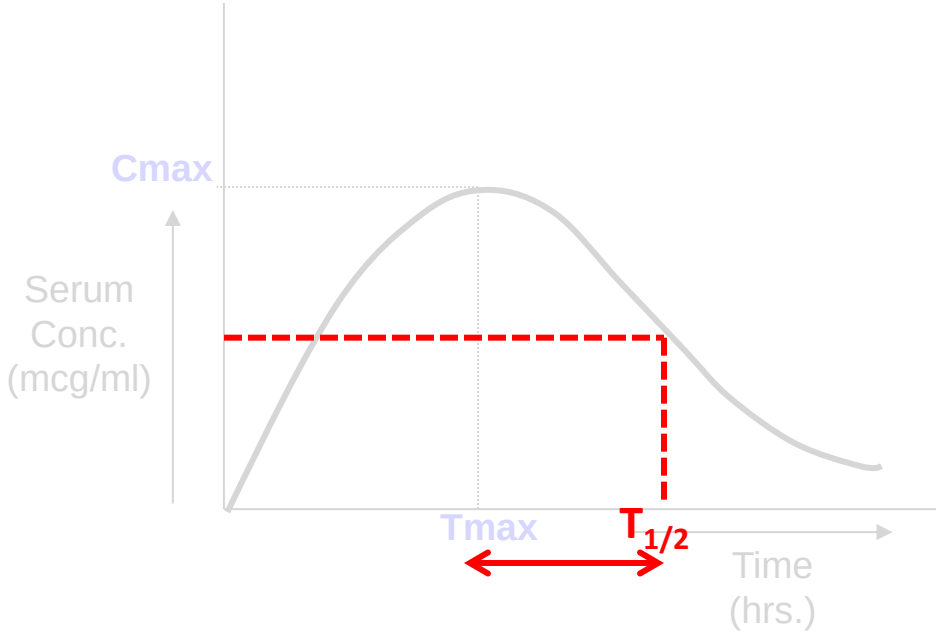
Maximum concentration of the drug achieved in blood (plasma)

Tmax

Time taken to achieve the peak plasma concentration

$T_{1/2}$ (plasma half life)

Time taken by drug for its peak plasma concentration to be reduced to half of its original value



Pharmacodynamics

"What drug does to the body"

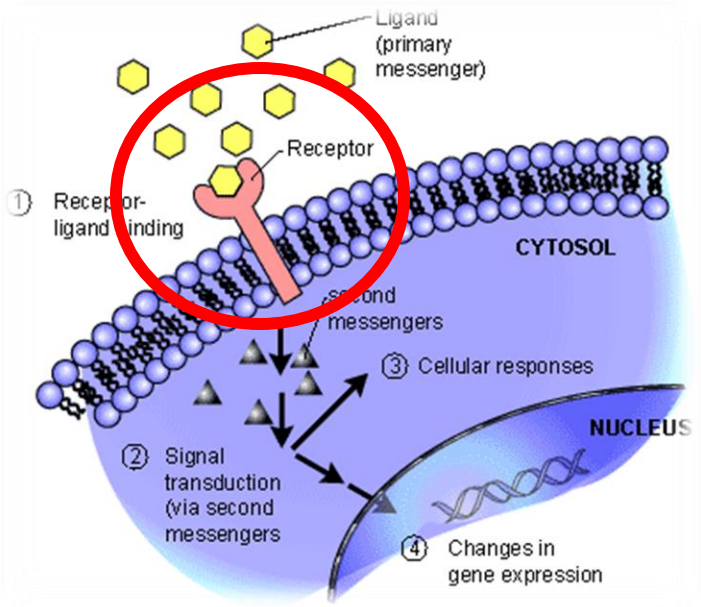
- Study of drug effects

Receptors

Defined as a macromolecule or binding site located on the surface or inside the effector cell

How do drugs act?

1) By chemical reactions
2) By action on enzymes
   - ✓ Activation
   - ✓ Inhibition
3) **By acting on receptors**



Combined effect of drugs

When two or more drugs are given simultaneously or in quick succession they may be

Additive/Complimentary | **2+2=4**

Effects of two drug add up

Amlodipine + Atenolol
Amlodipine + Hydrochlorothiazide

Synergism | **2+2=5**

Action of one drug is facilitated or increased by the other

Alprazolam + Alcohol

Antagonism | **2+2=3**

One drug decreases or inhibits action of another

Iron + Calcium

Routes of drug administration

A) Topical

- On skin or mucous membrane
- E.g. creams, ointment, powders, eye drops, eardrops etc

B) Oral (enteral)

- By oral route
- e.g. tablets, capsules, syrups etc.

C) Parenteral

- Intravenous
- Intramuscular
- Subcutaneous

1. Introduction to pharmacology

2. Human anatomy and physiology

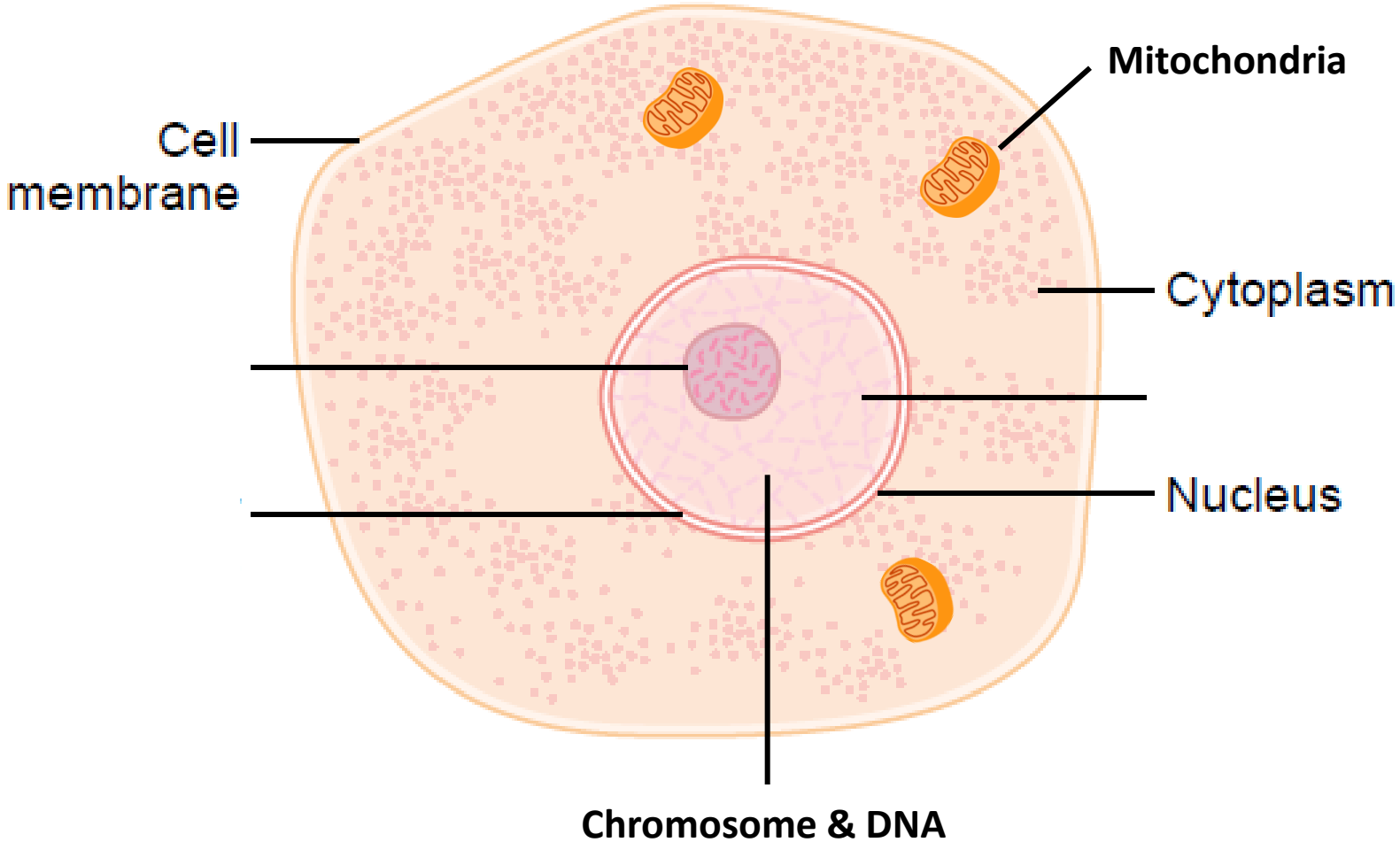
Anatomy

Branch of biology concerned with the study of the structure of organisms and their parts

Physiology

Branch of biology dealing with the functions of organs

A cell


Mitochondria
Cell membrane
Cytoplasm
Nucleus
Chromosome & DNA

Body systems

The human body systems are as follows:

-- Nervous system

-- Respiratory system

-- Excretory system

-- Musculoskeletal system

-- Reproductive system

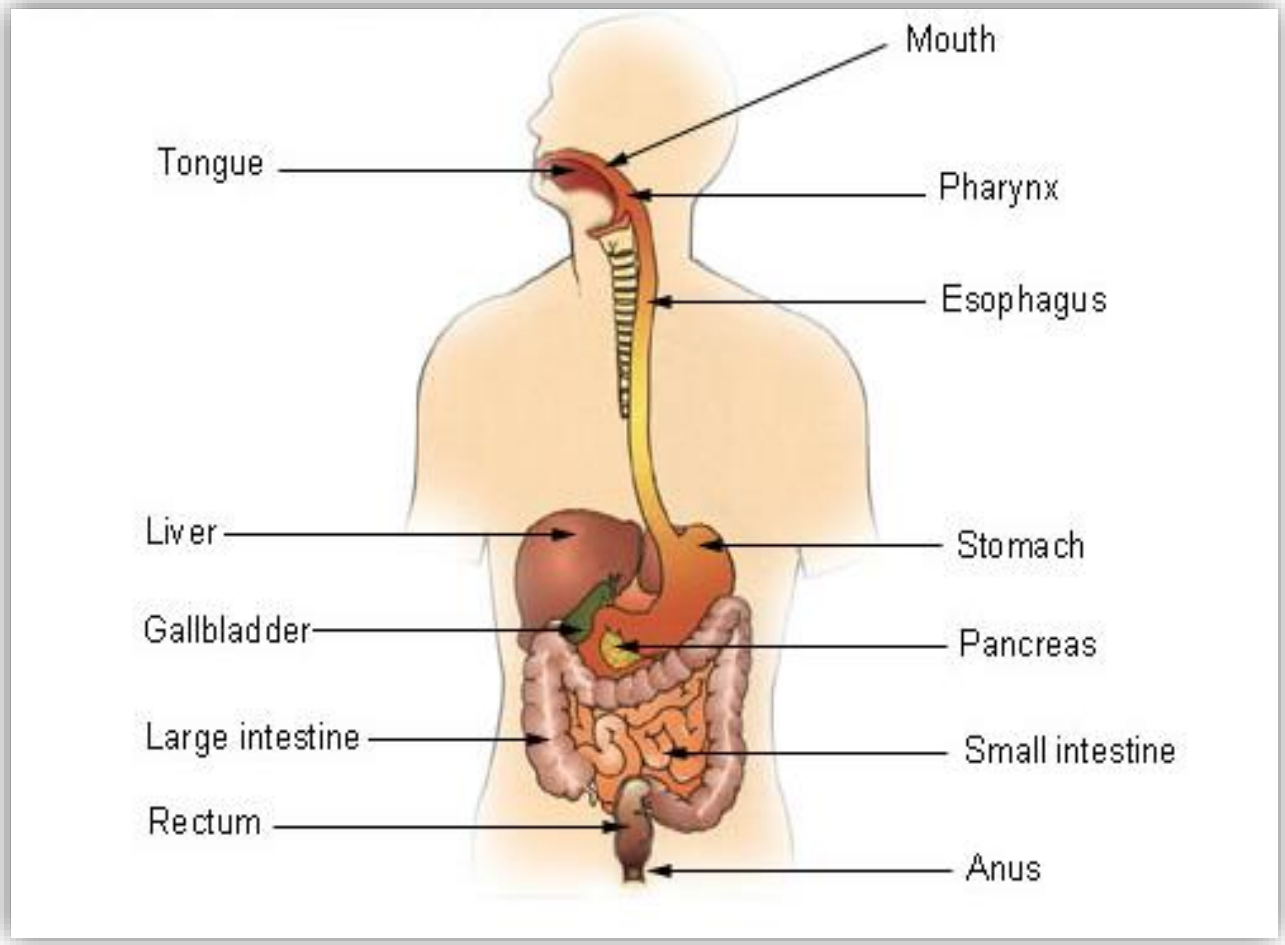
-- Digestive system

-- Cardiovascular System

-- Endocrine system

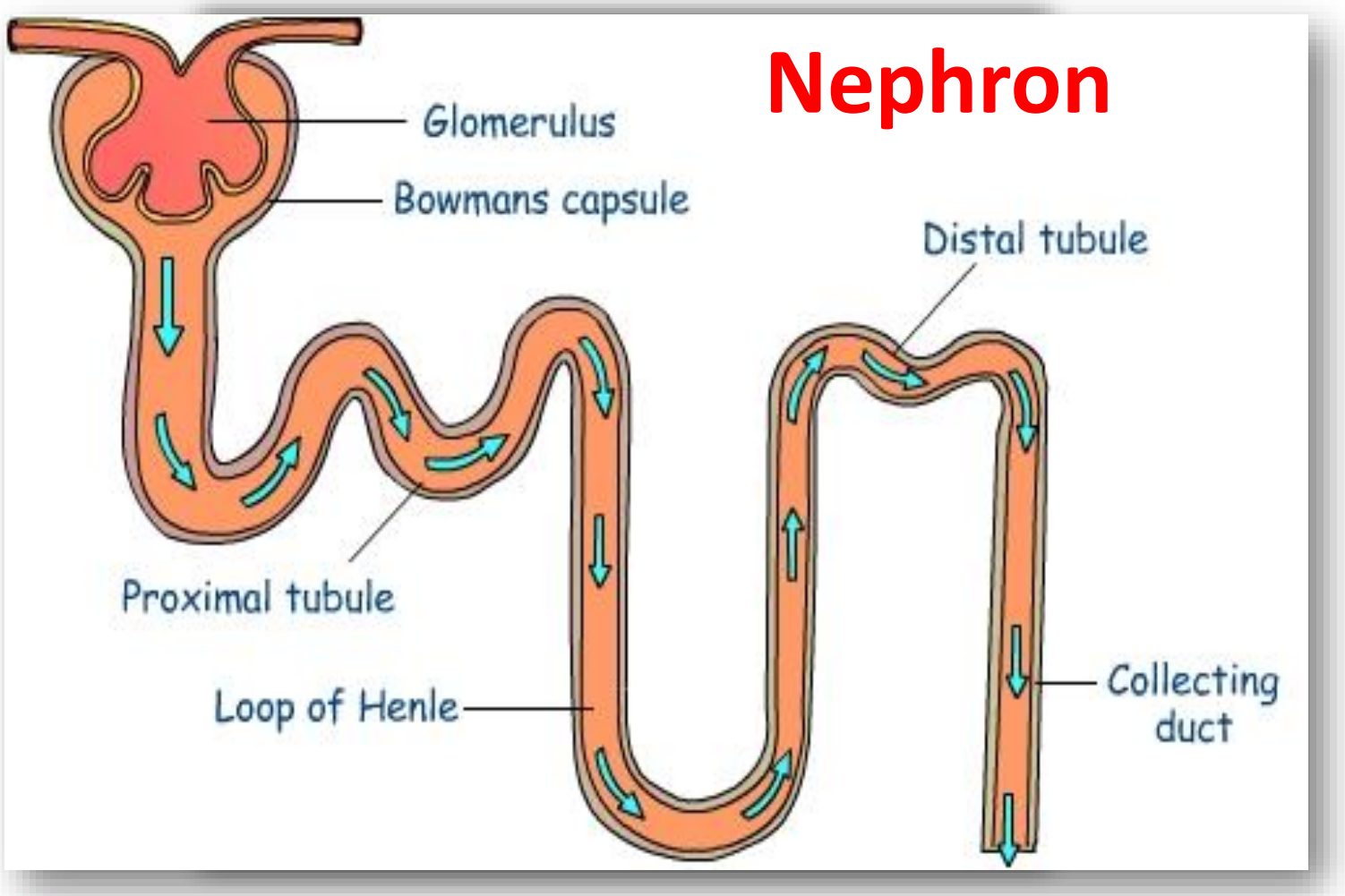
The Digestive System

Purpose: To convert food particles into simpler that can be absorbed into the bloodstream and used by the body and throw the waste product out of the body



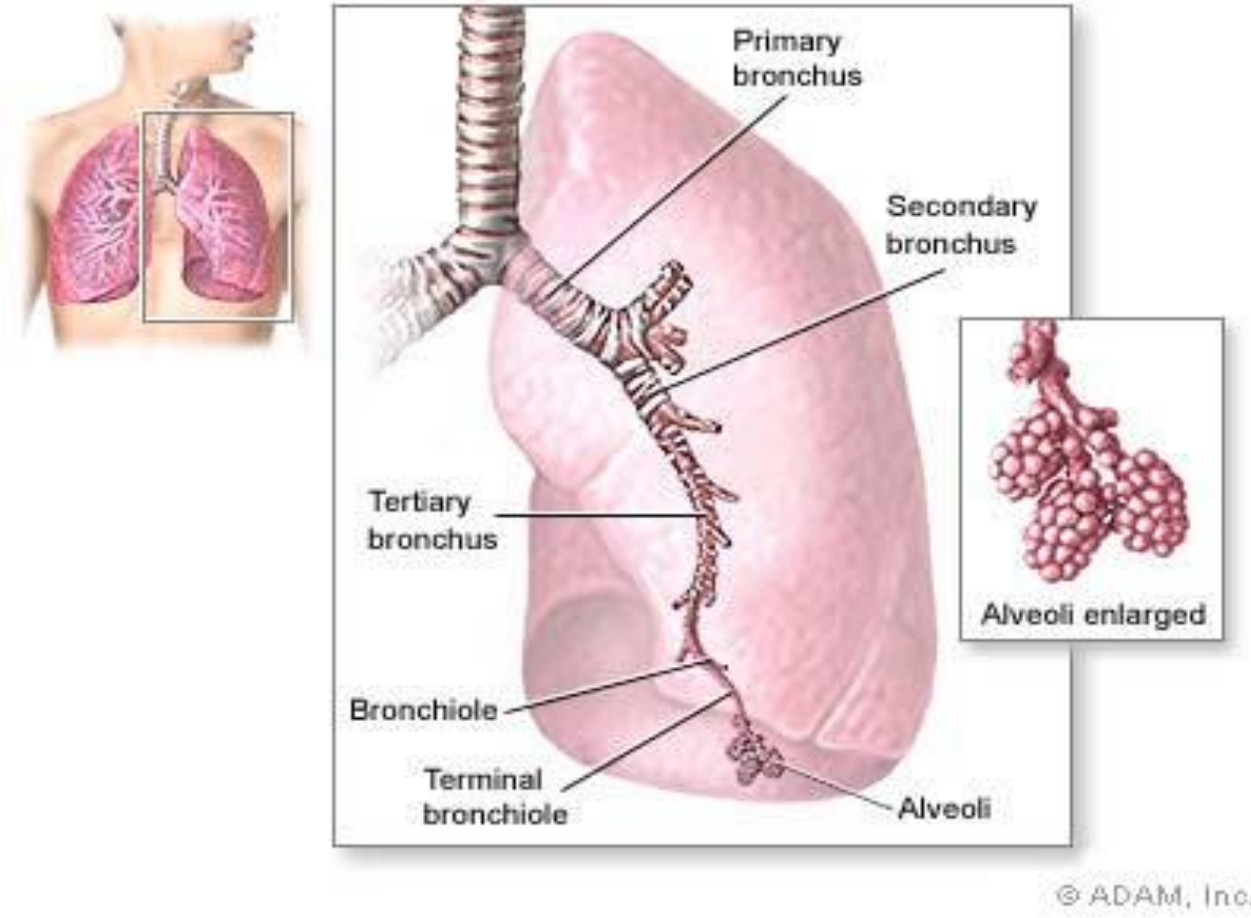
The Excretory System

Purpose: To throw the waste products from the blood and re-absorb important ions



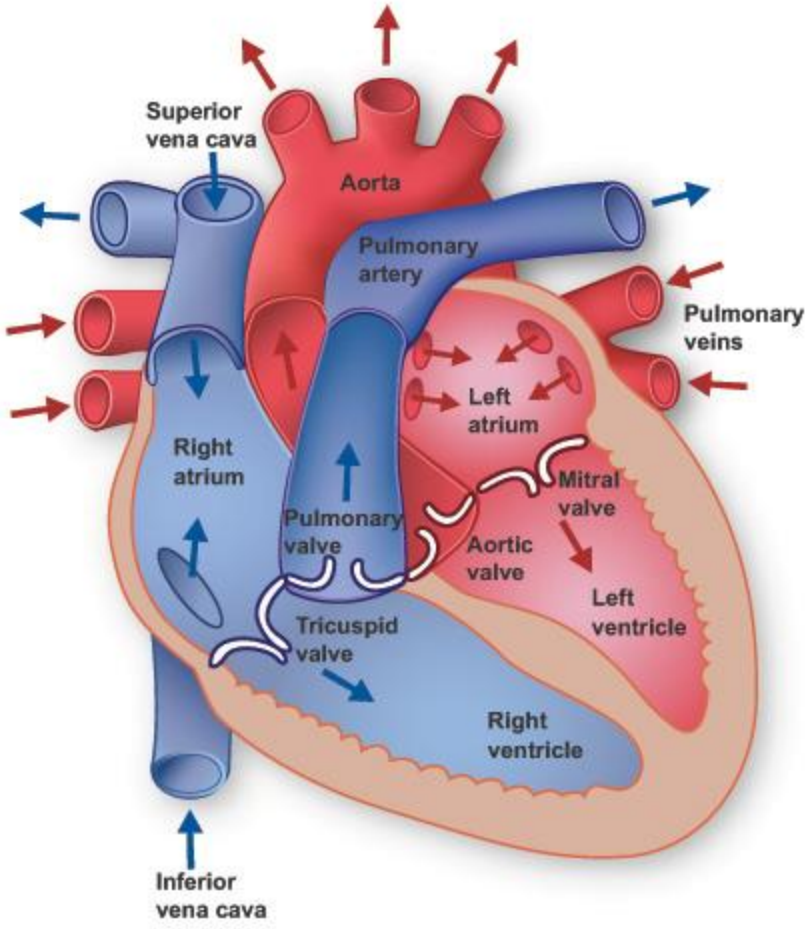
The Respiratory System

Purpose: To provide the body with a fresh supply of oxygen for cellular respiration and remove the waste product carbon dioxide



The Circulatory System

Purpose: To deliver oxygenated blood to the various cells and organ systems

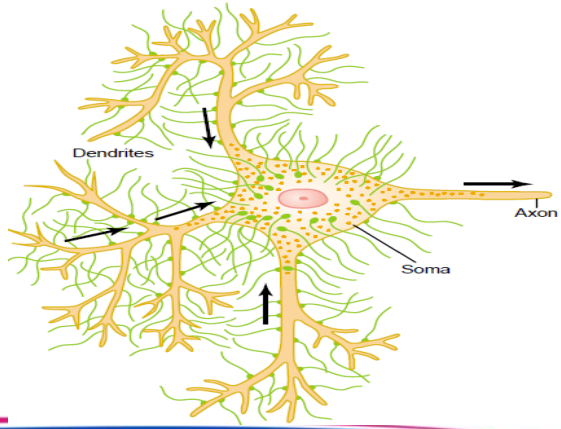


The Nervous System

Purpose: To coordinate the body's response to changes in its internal and external environment

Spinal Nerves

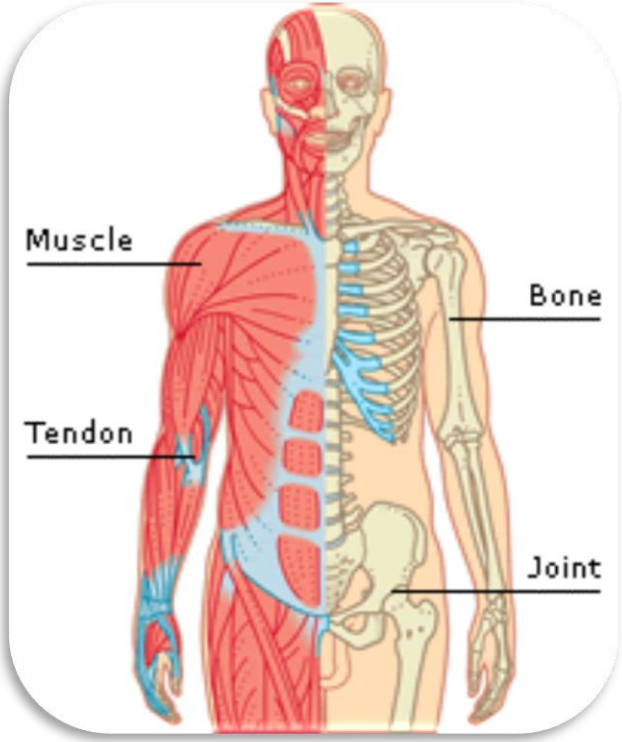
Neuron



The Musculo-Skeletal System

Purpose: To provide structure and support to the human body

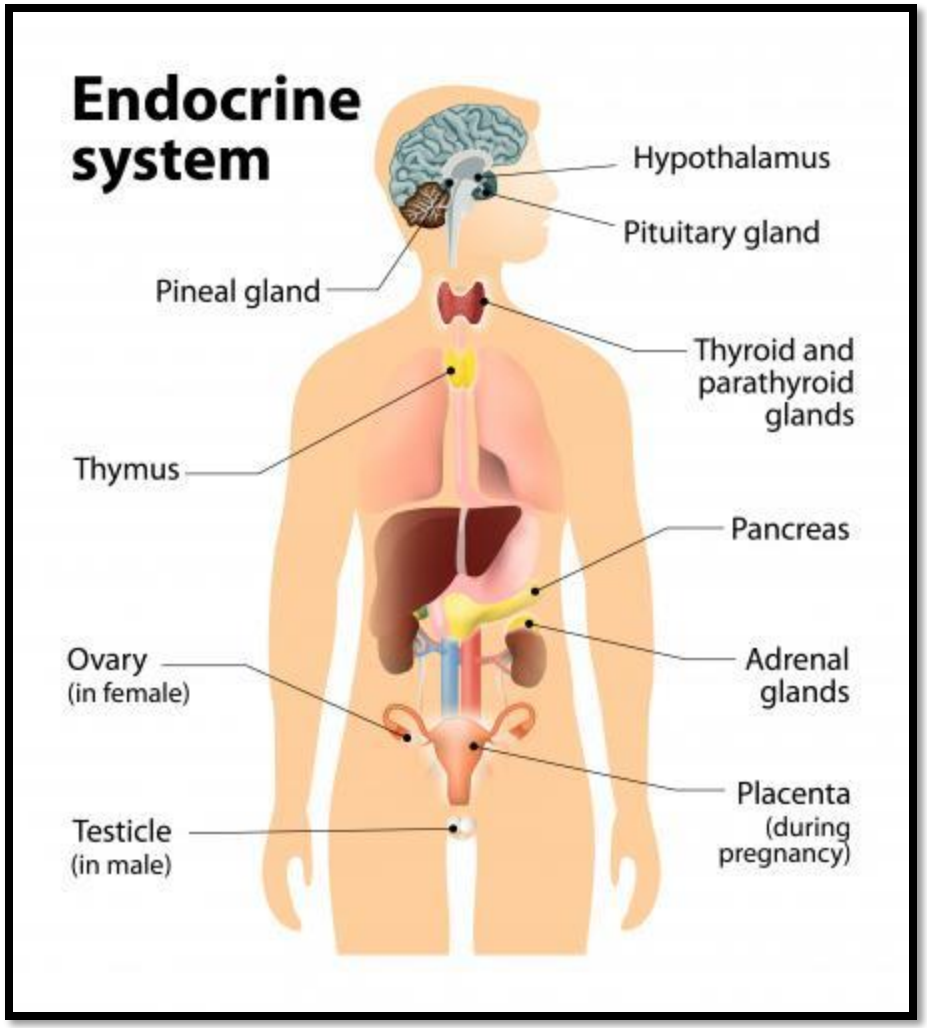
Consist of bones and muscles



The Endocrine System

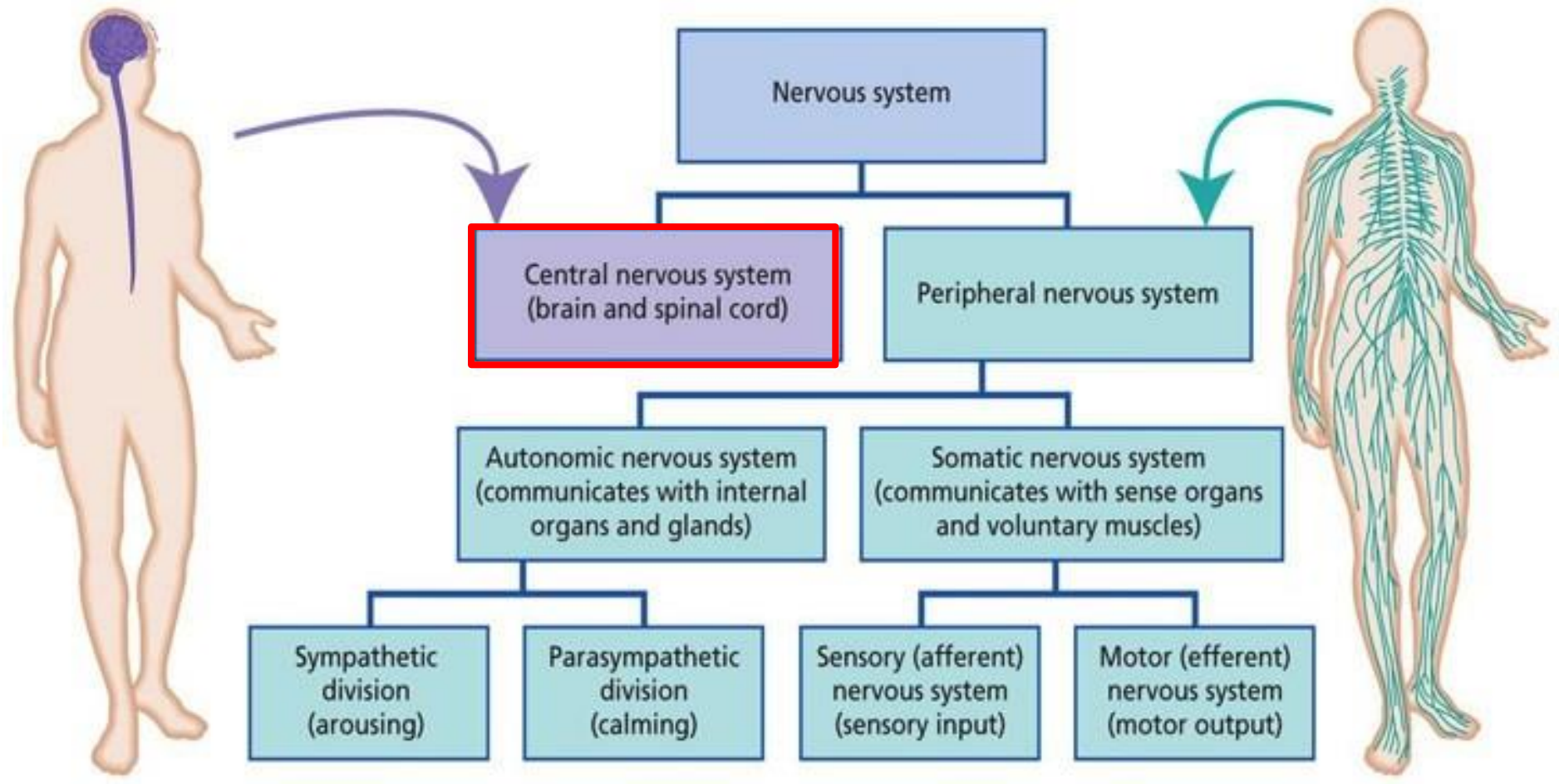
Purpose: To control growth, development, metabolism and reproduction through the production and secretion of hormones

Hormone – Chemical substance secreted by an endocrine gland into bloodstream that affects the function of another cell

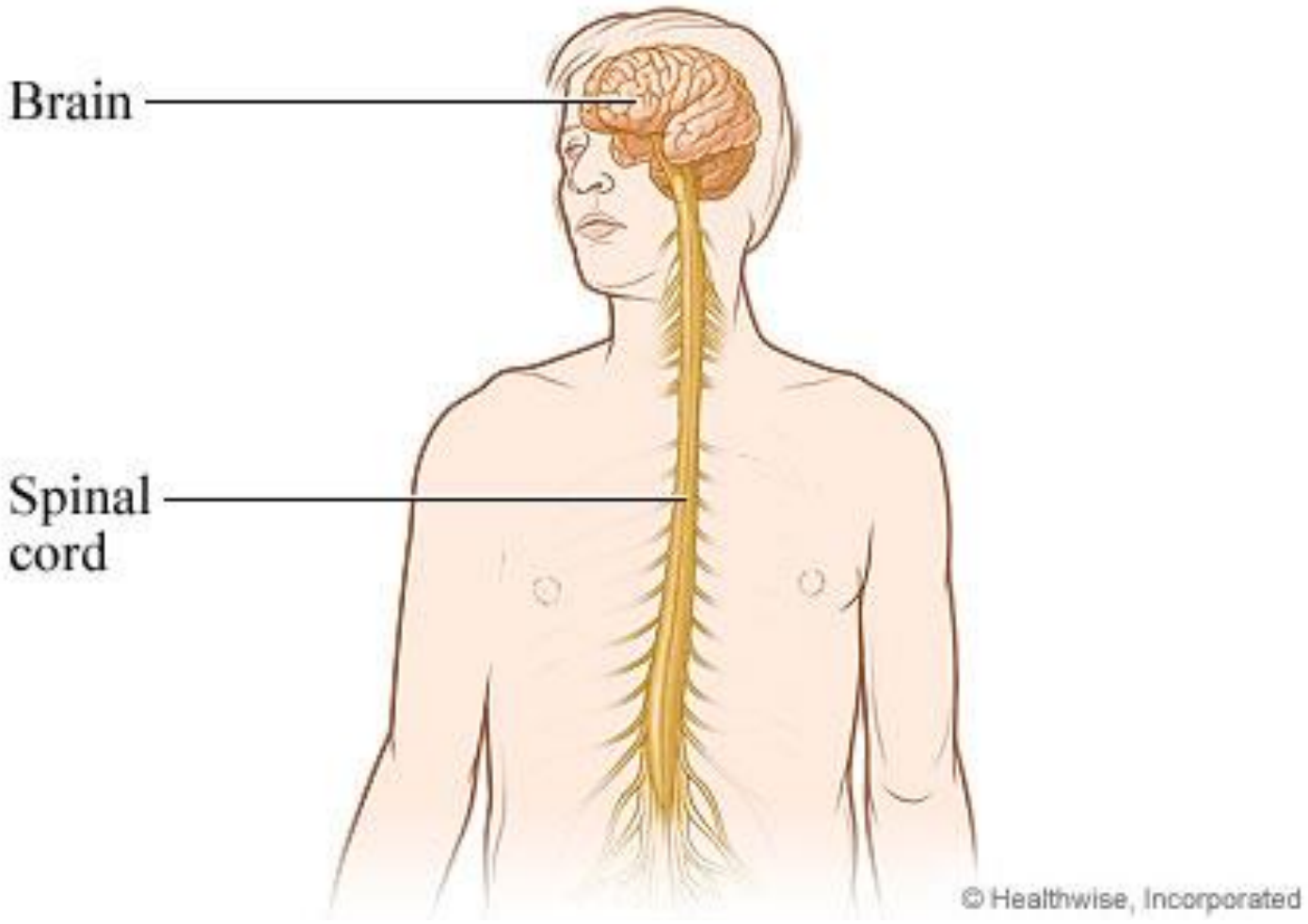


Nervous System

Nervous System Classification

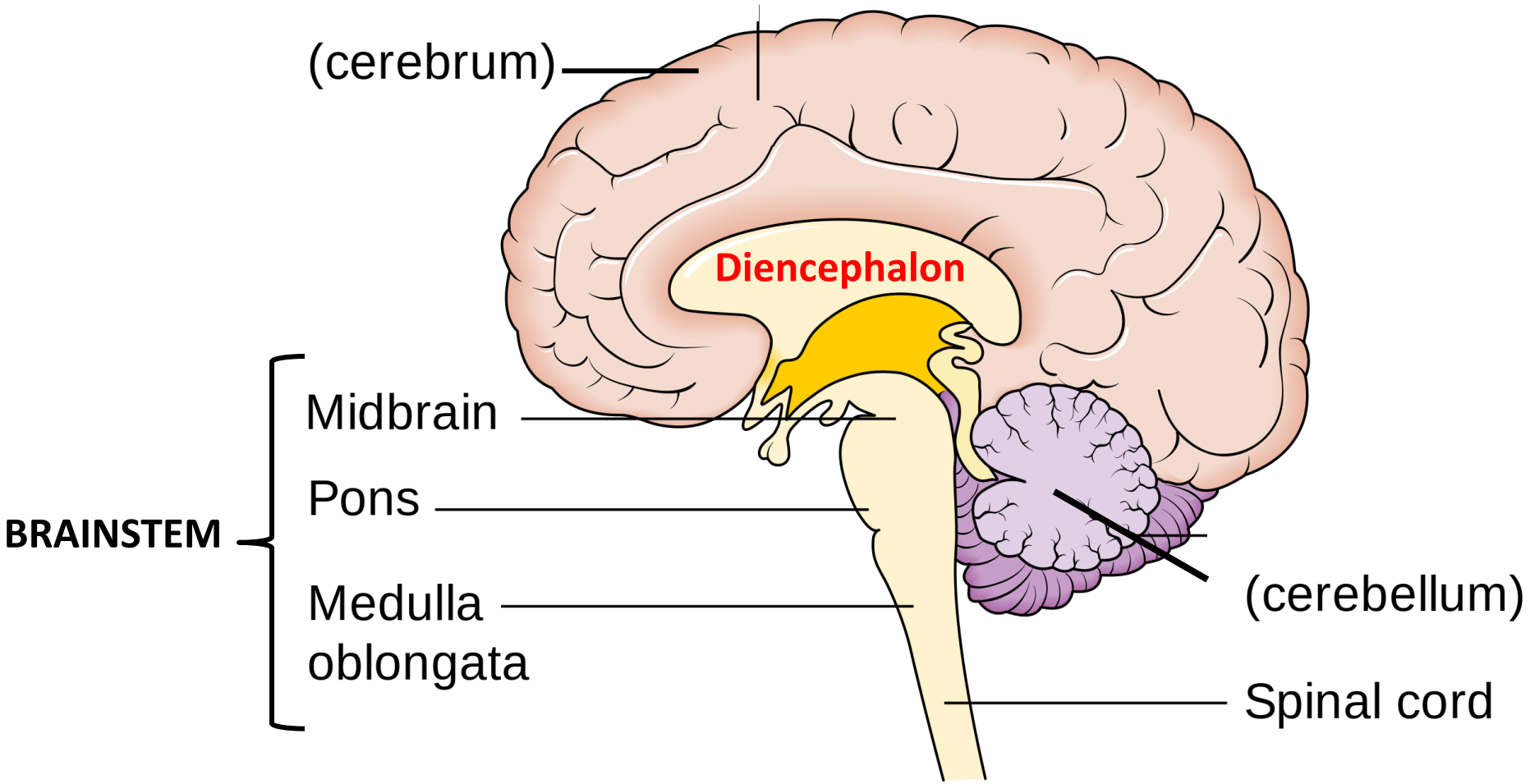


Central Nervous System

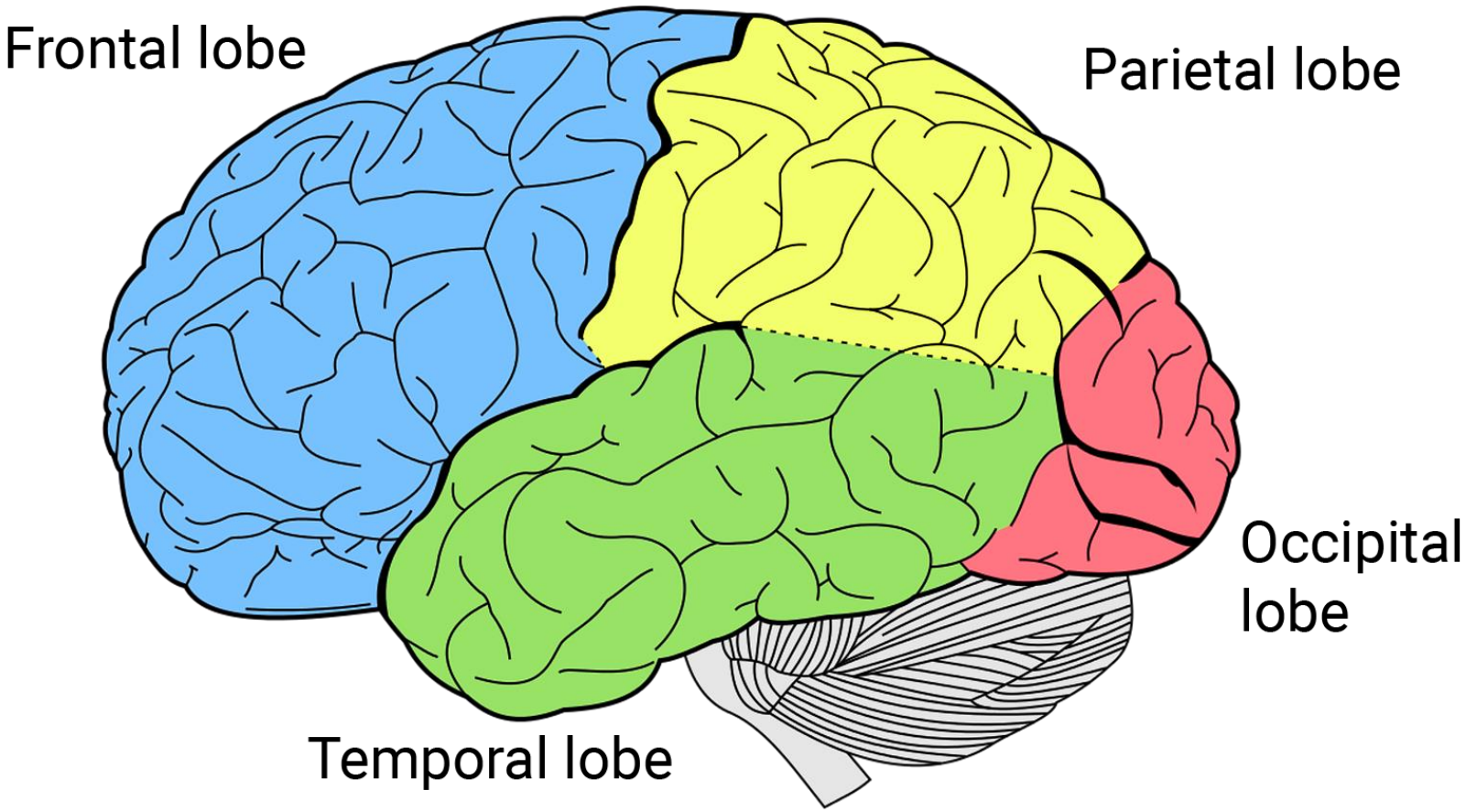


Brain

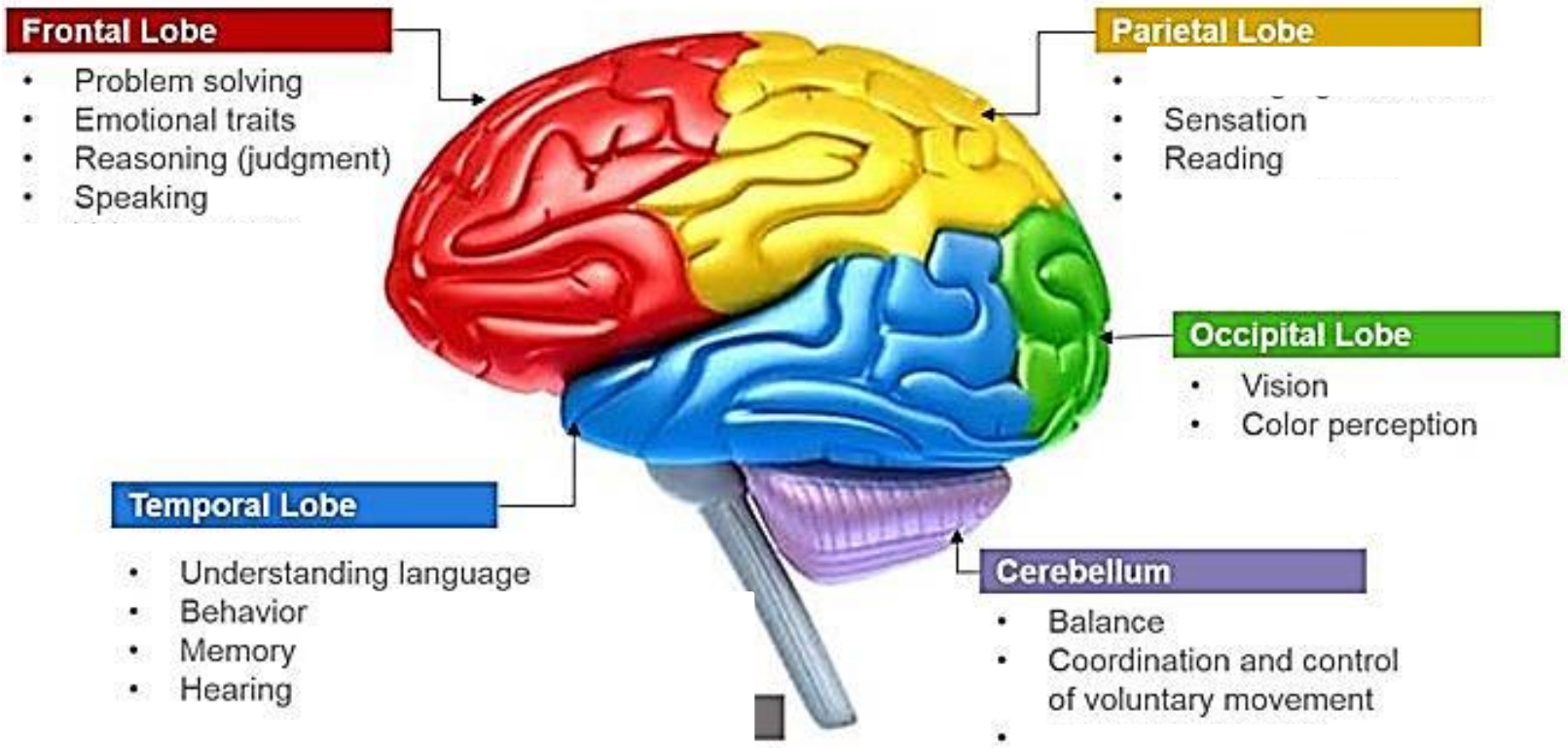
Parts of the Brain



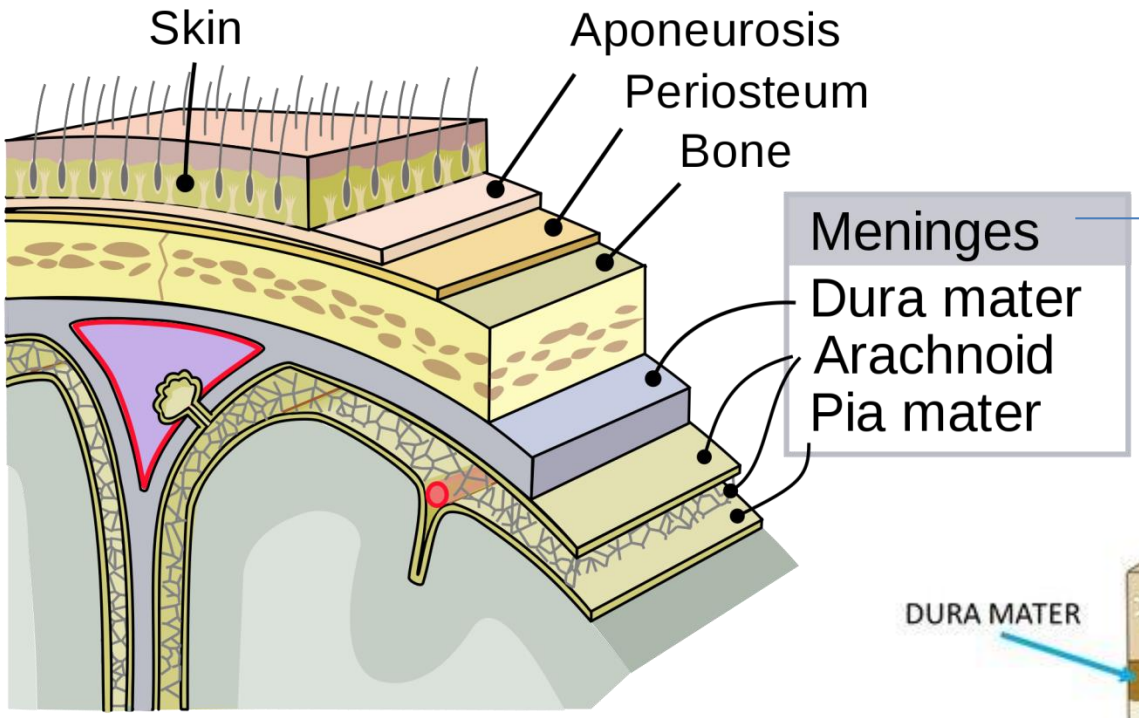
Parts of Cerebral Cortex



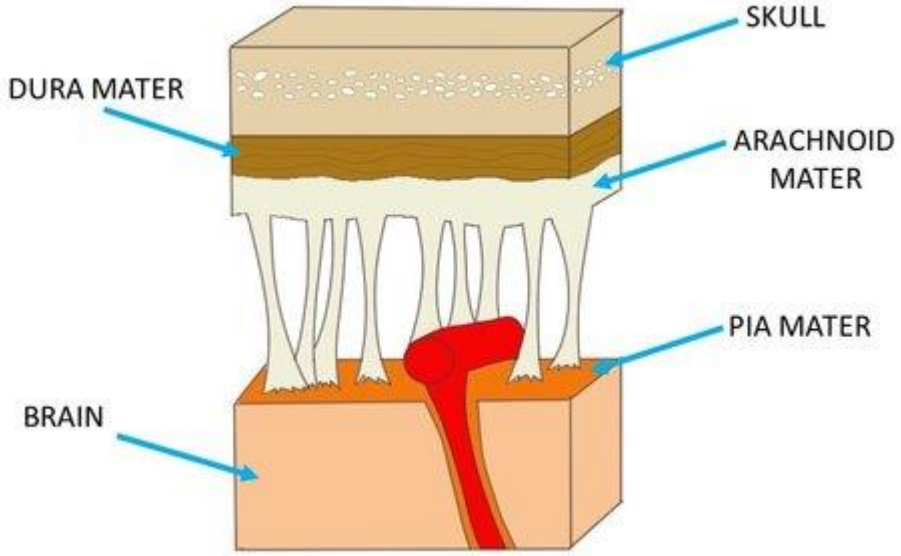
Functions of Cerebrum & Cerebellum



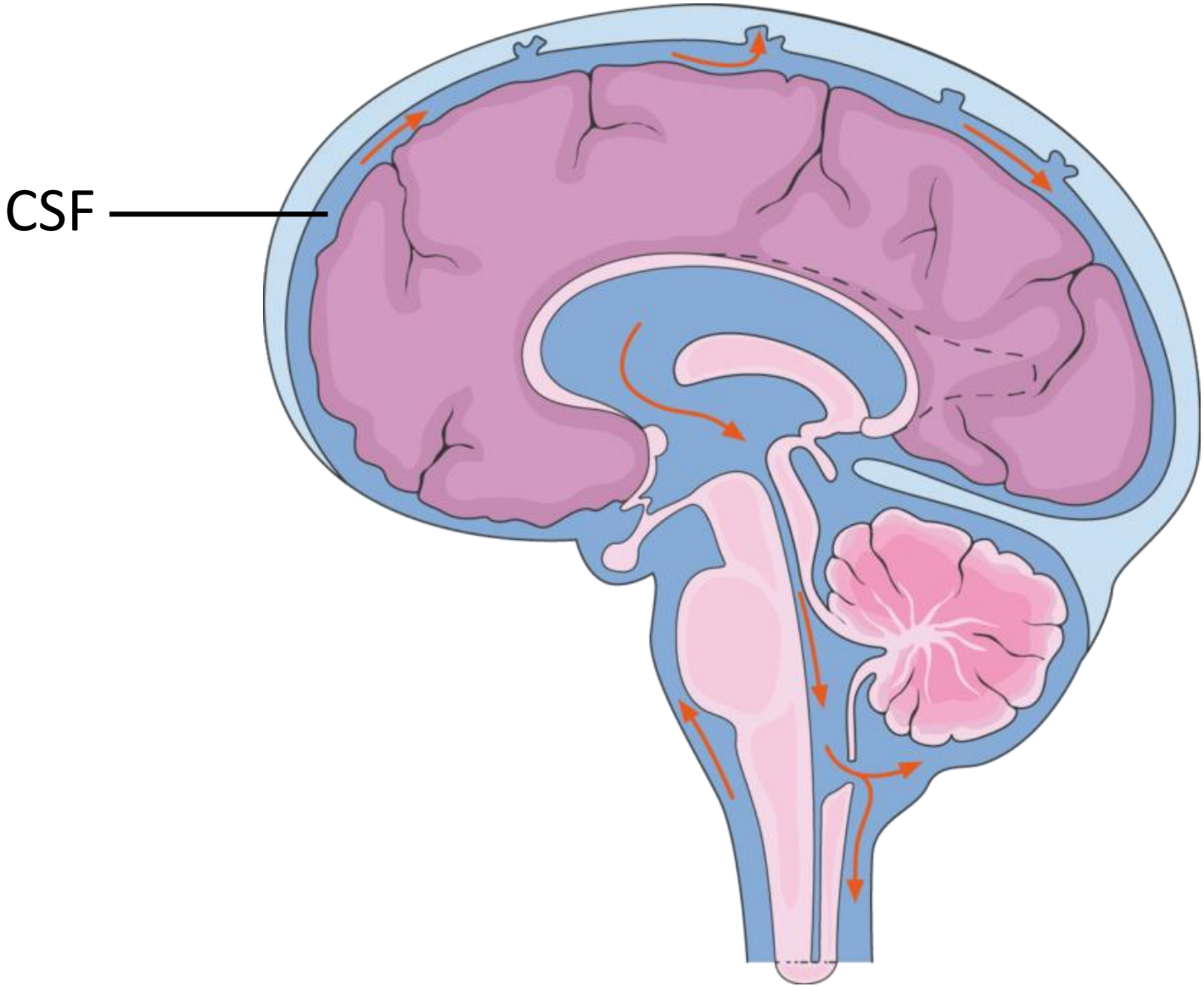
Meninges and Cerebro-Spinal Fluid



Covering of Brain & Spinal cord

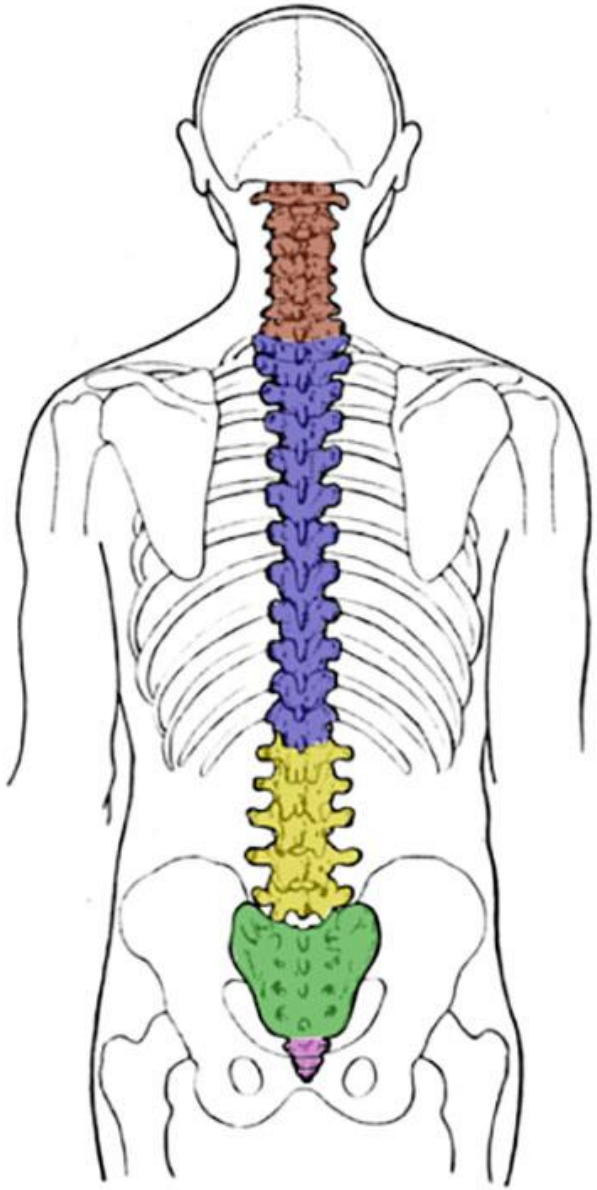


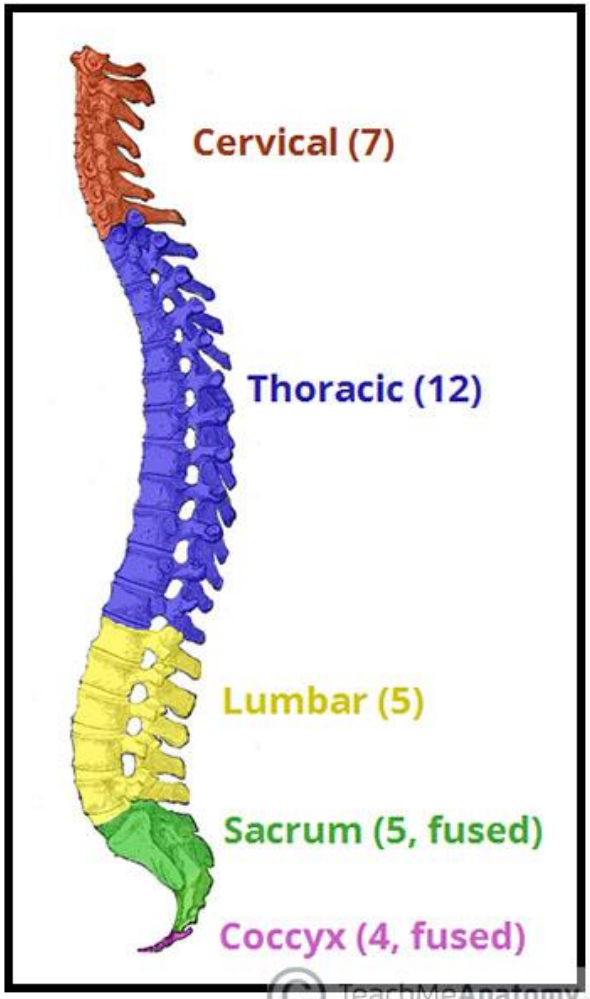
Meninges and Cerebro-Spinal Fluid



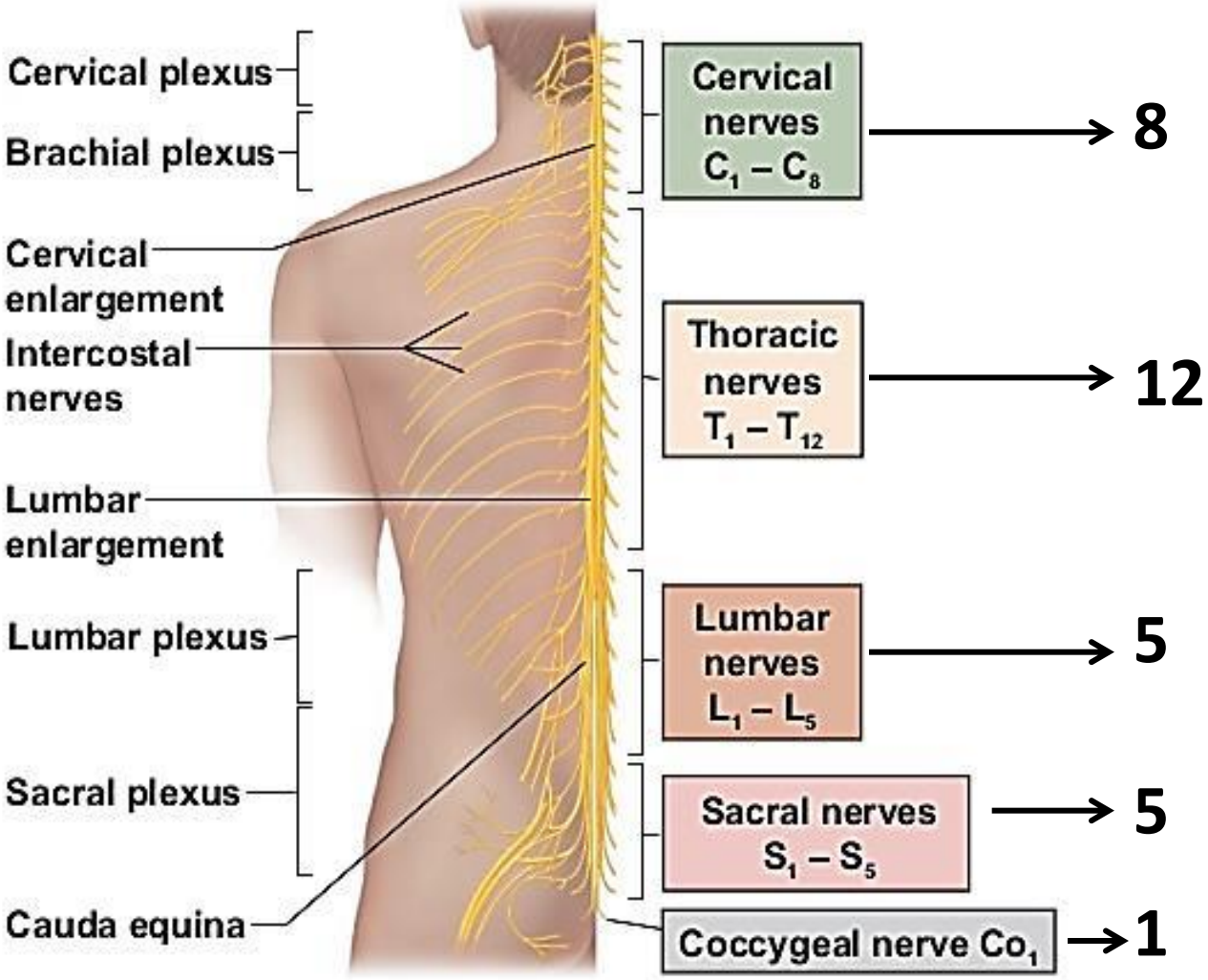
Spinal Cord

Vertebrae (33)

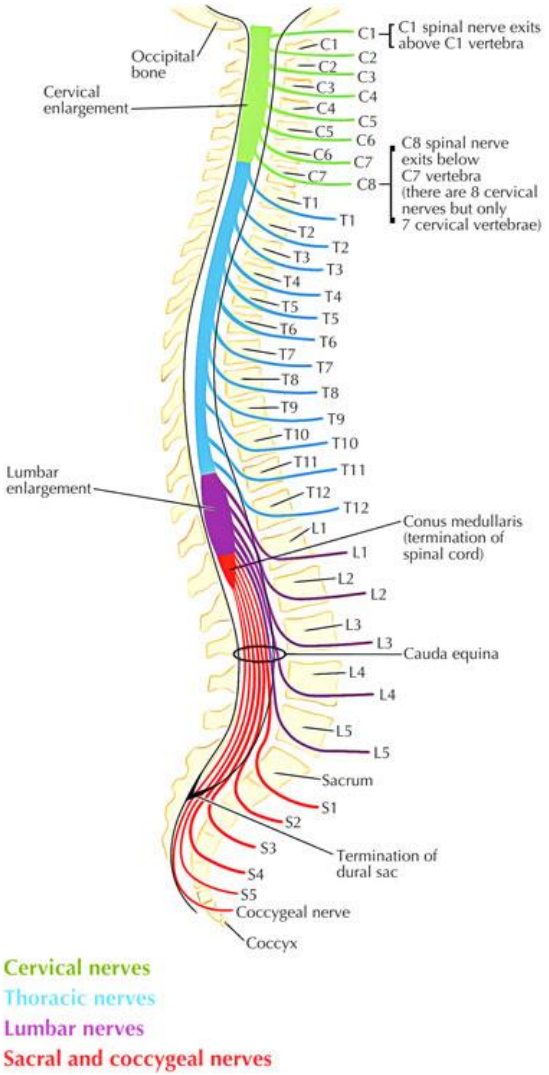




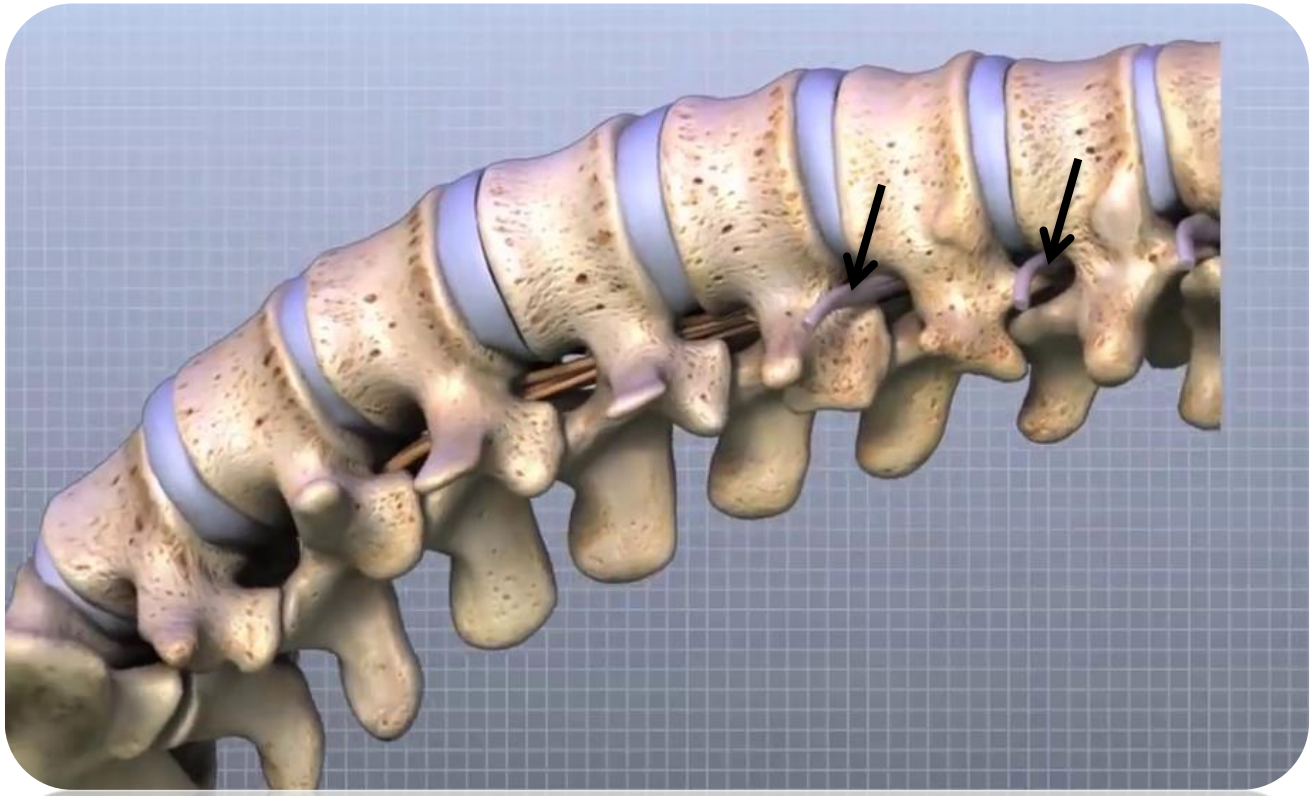
Spinal Nerves



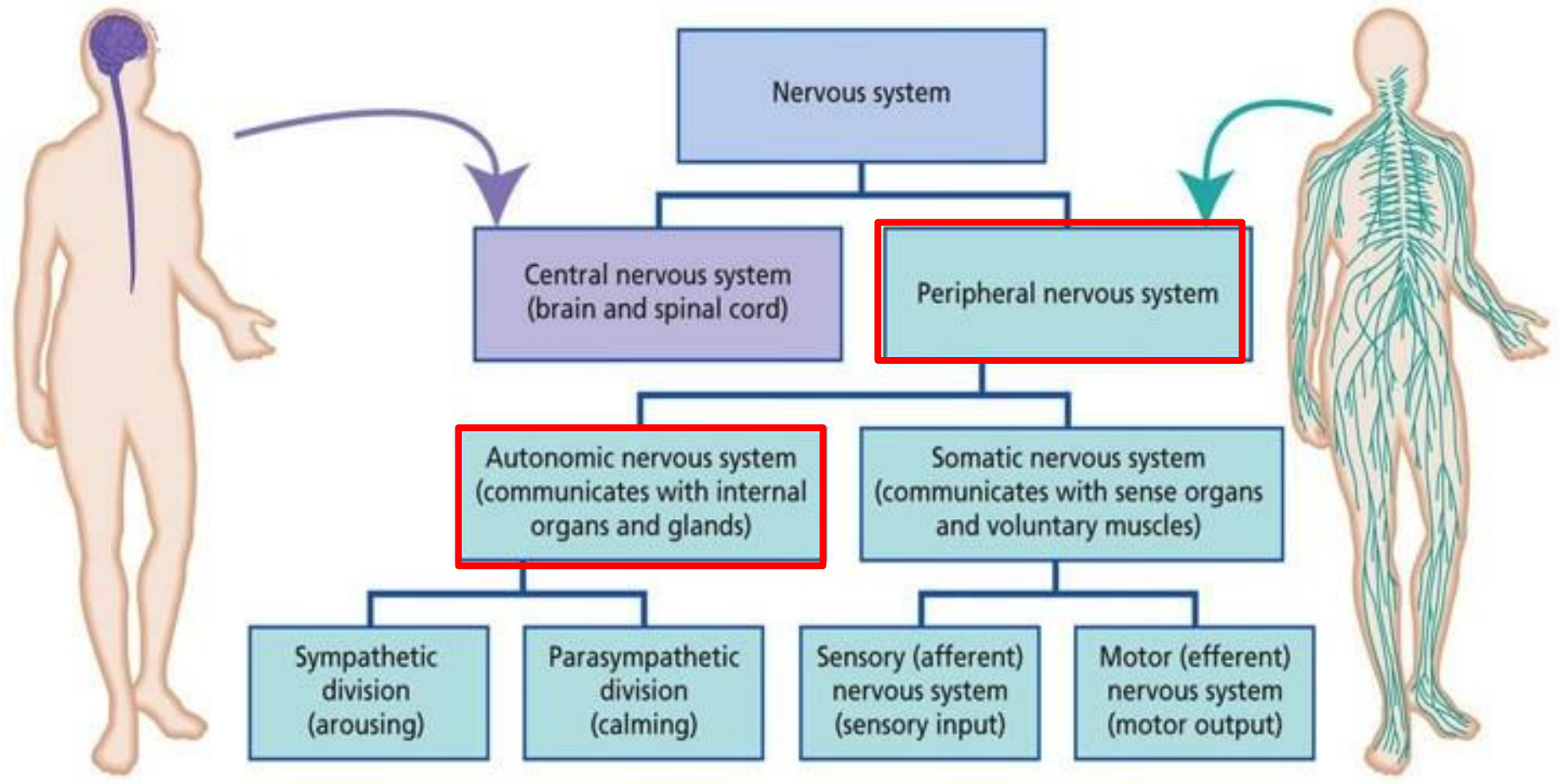
Spinal nerves



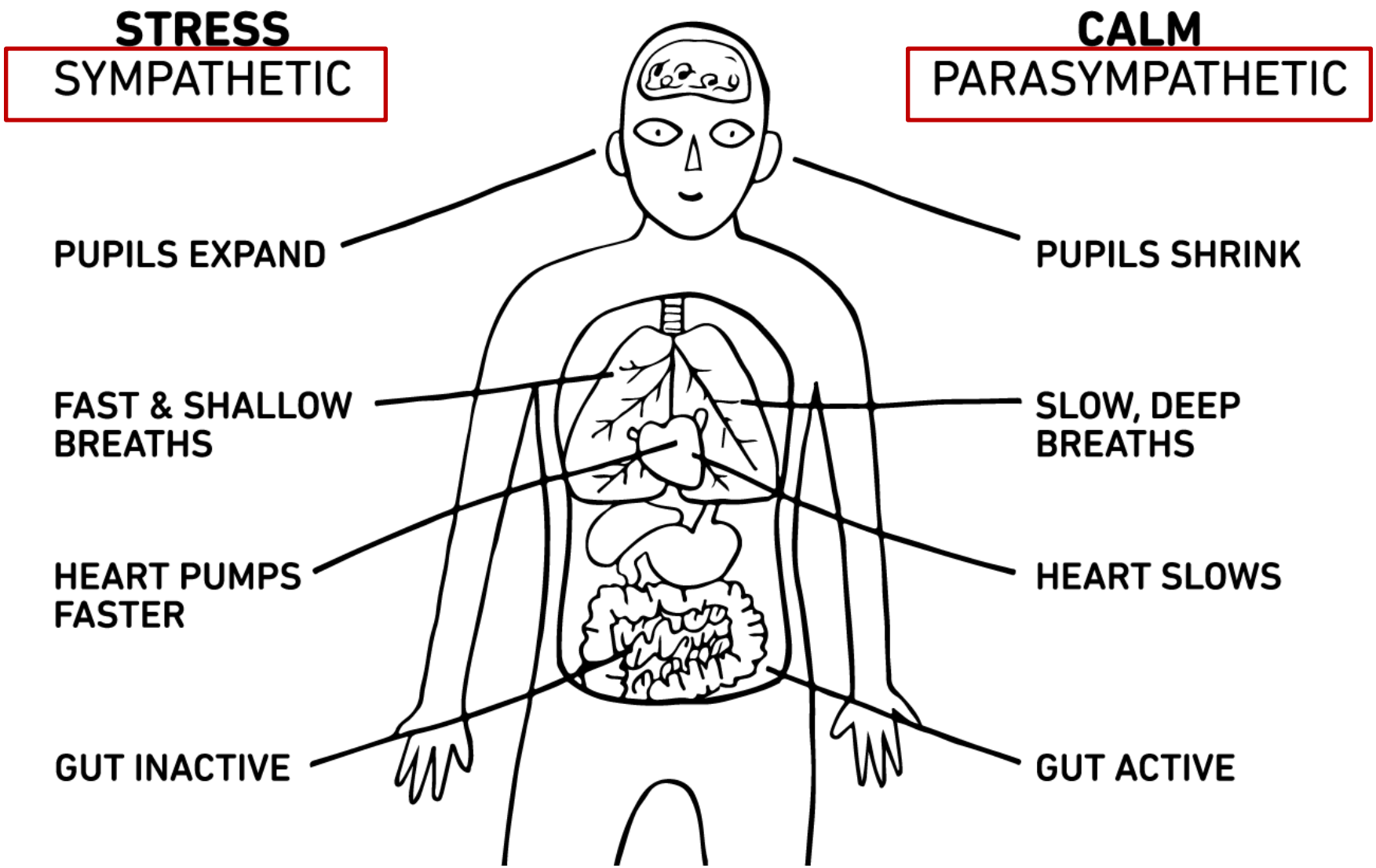
Spinal nerves



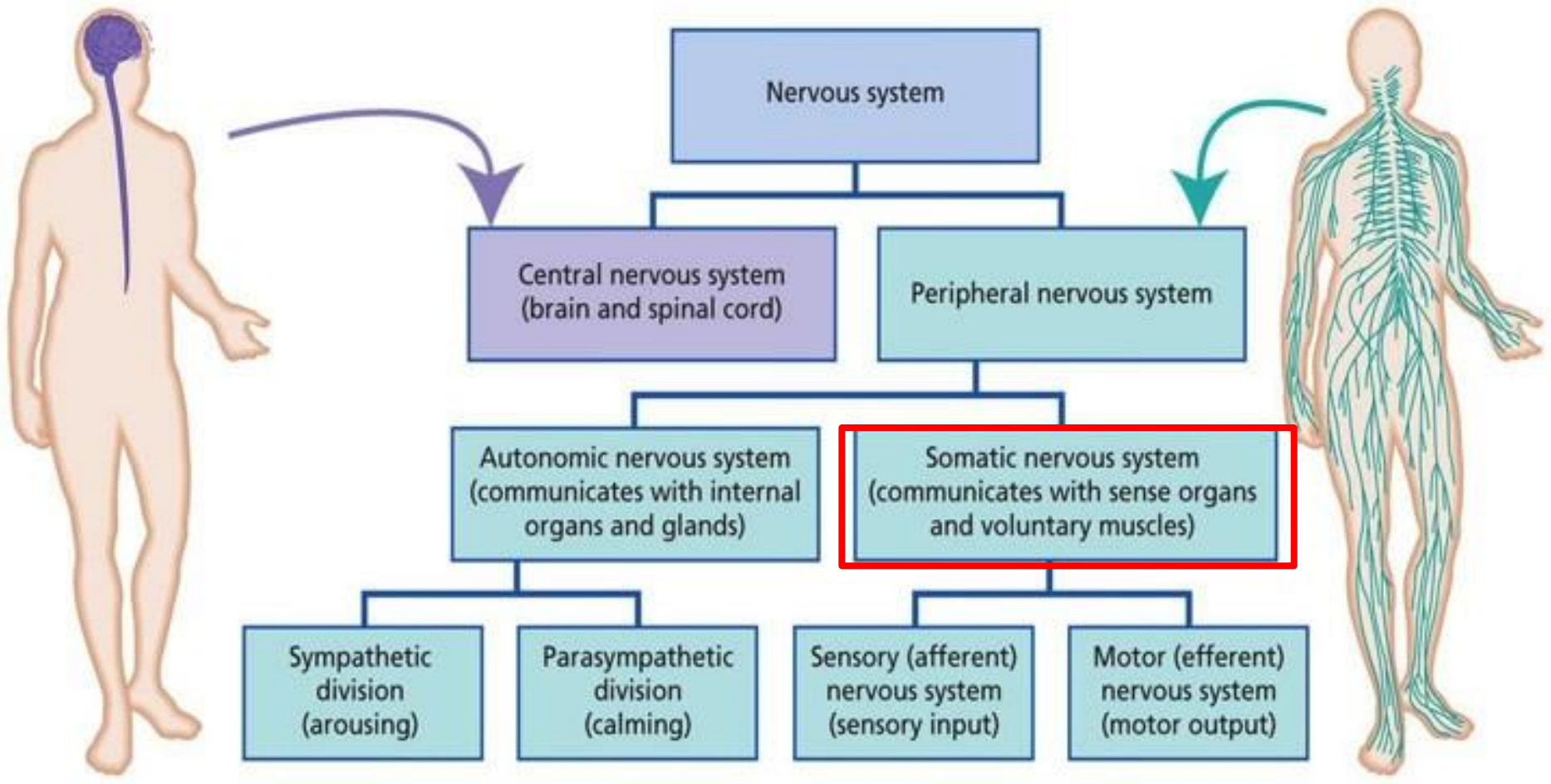
Nervous System Classification



Autonomic Nervous System

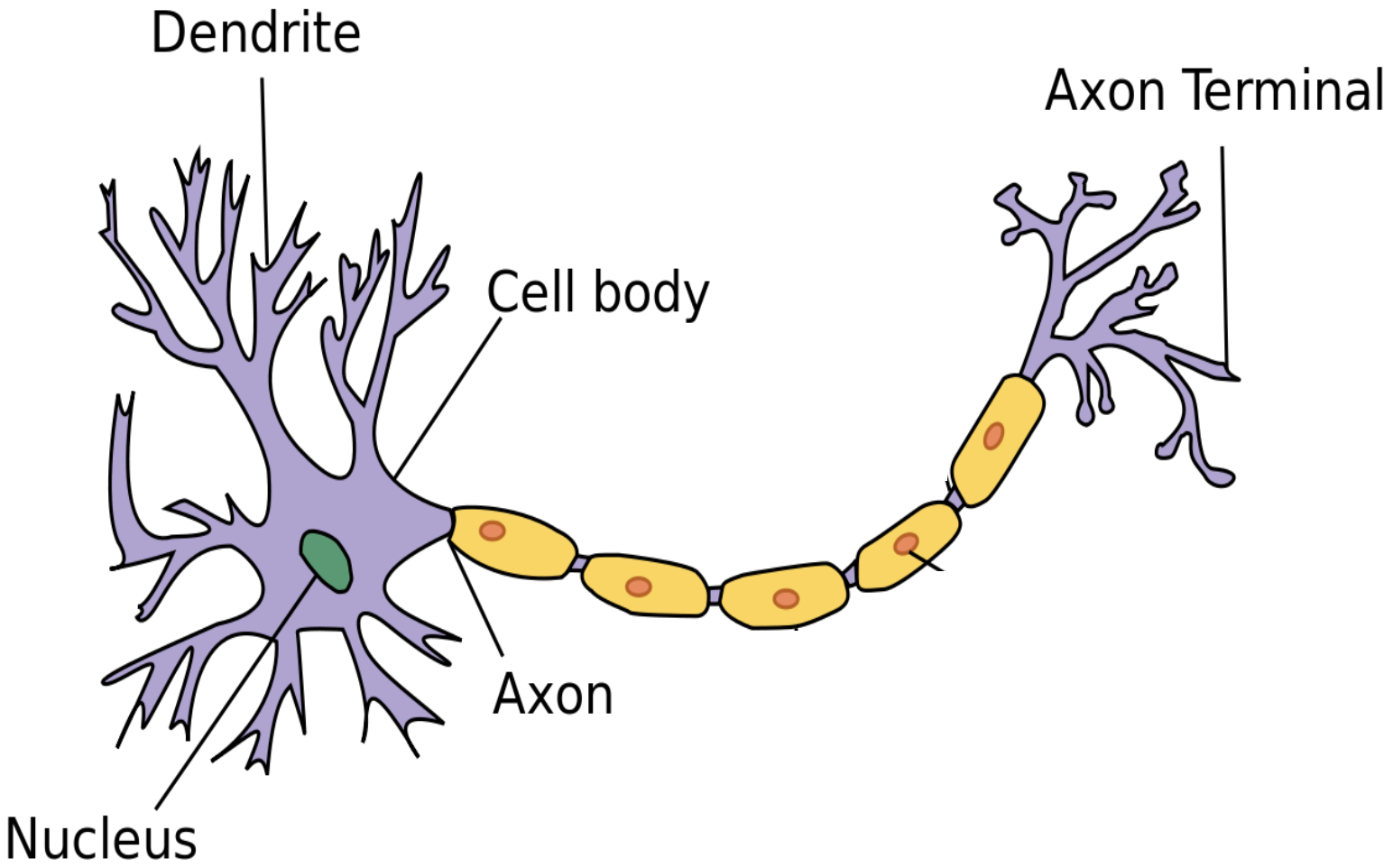


Nervous System Classification



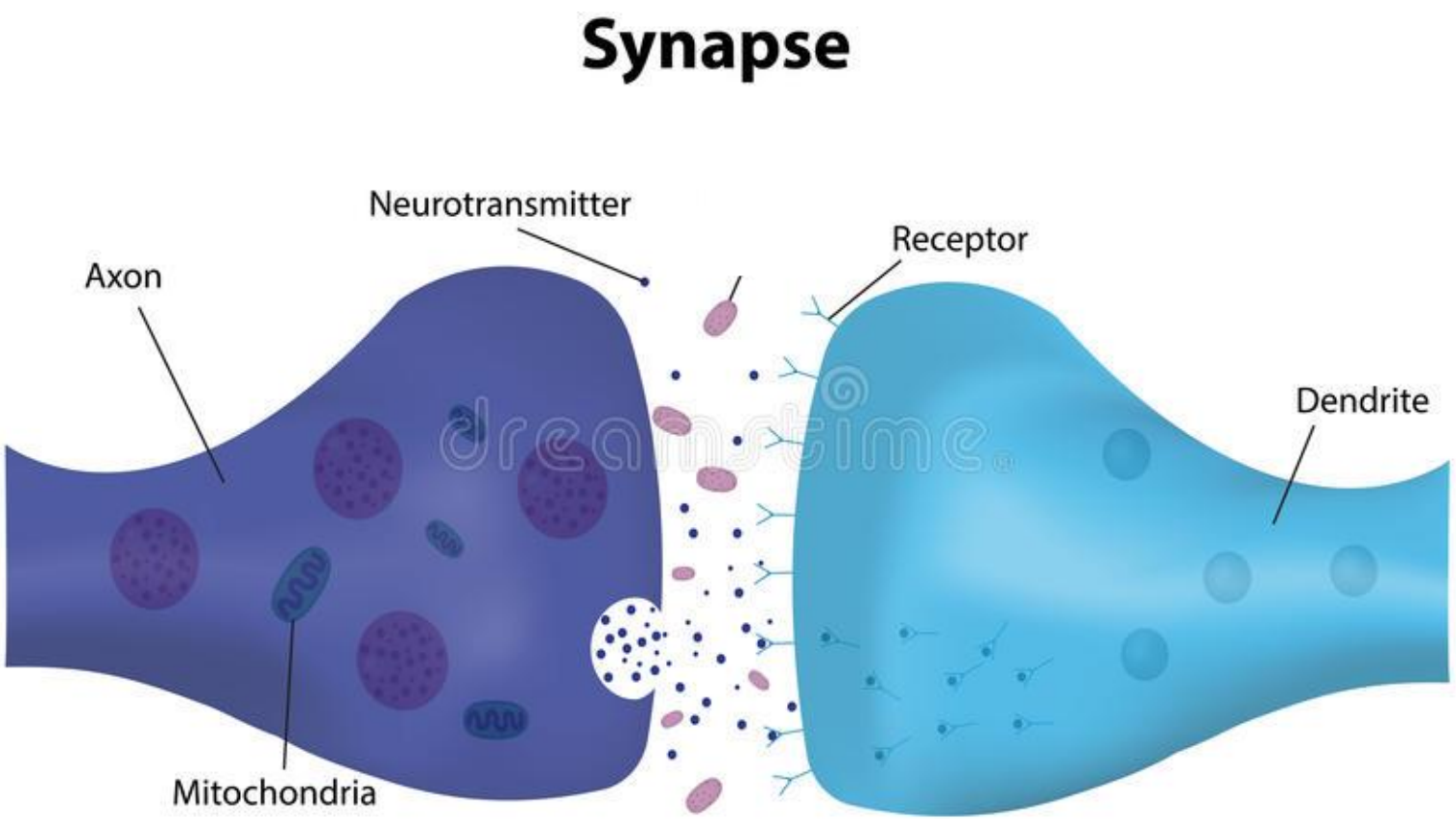
- Video of Nervous system

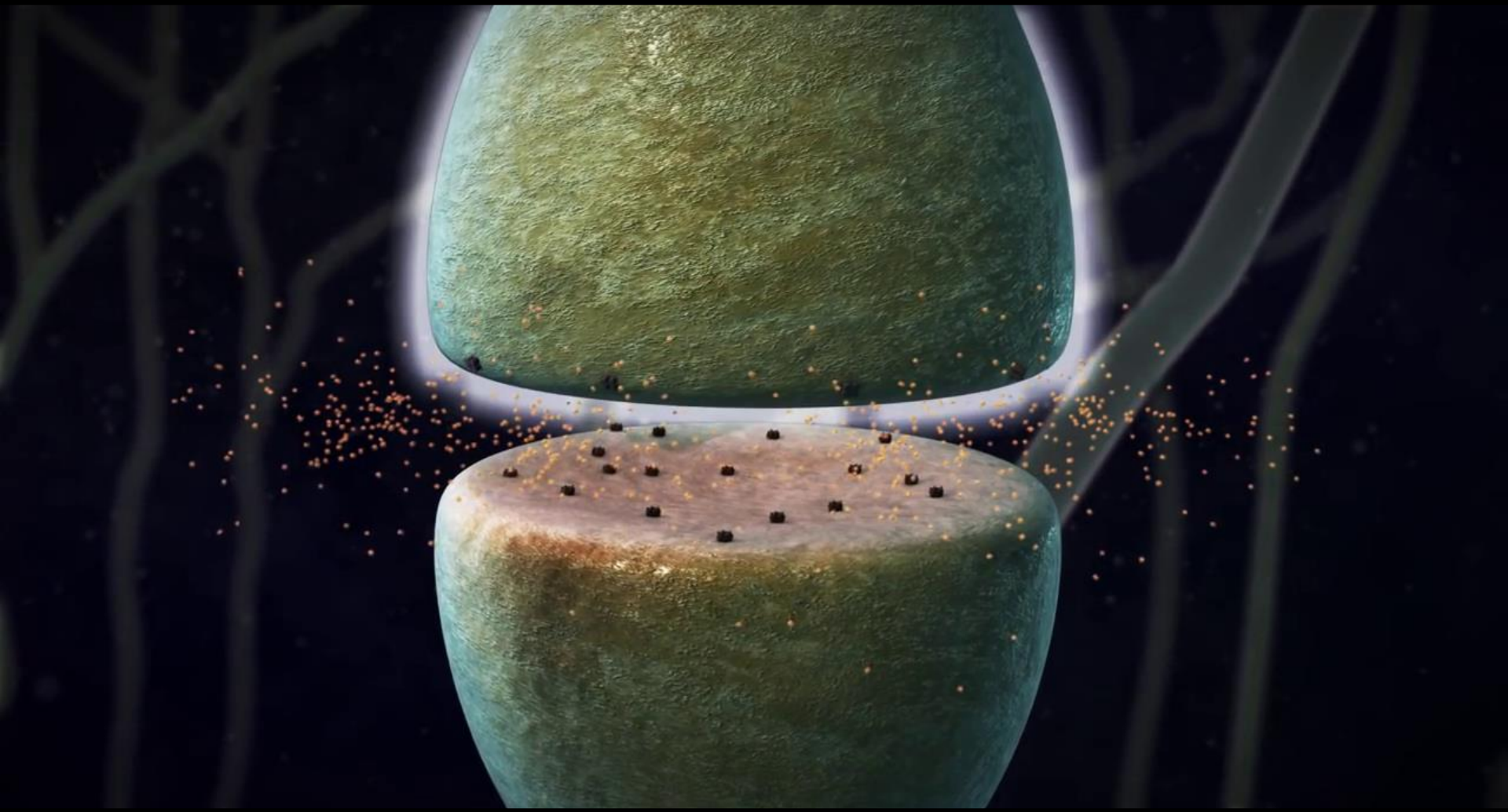
Neuron

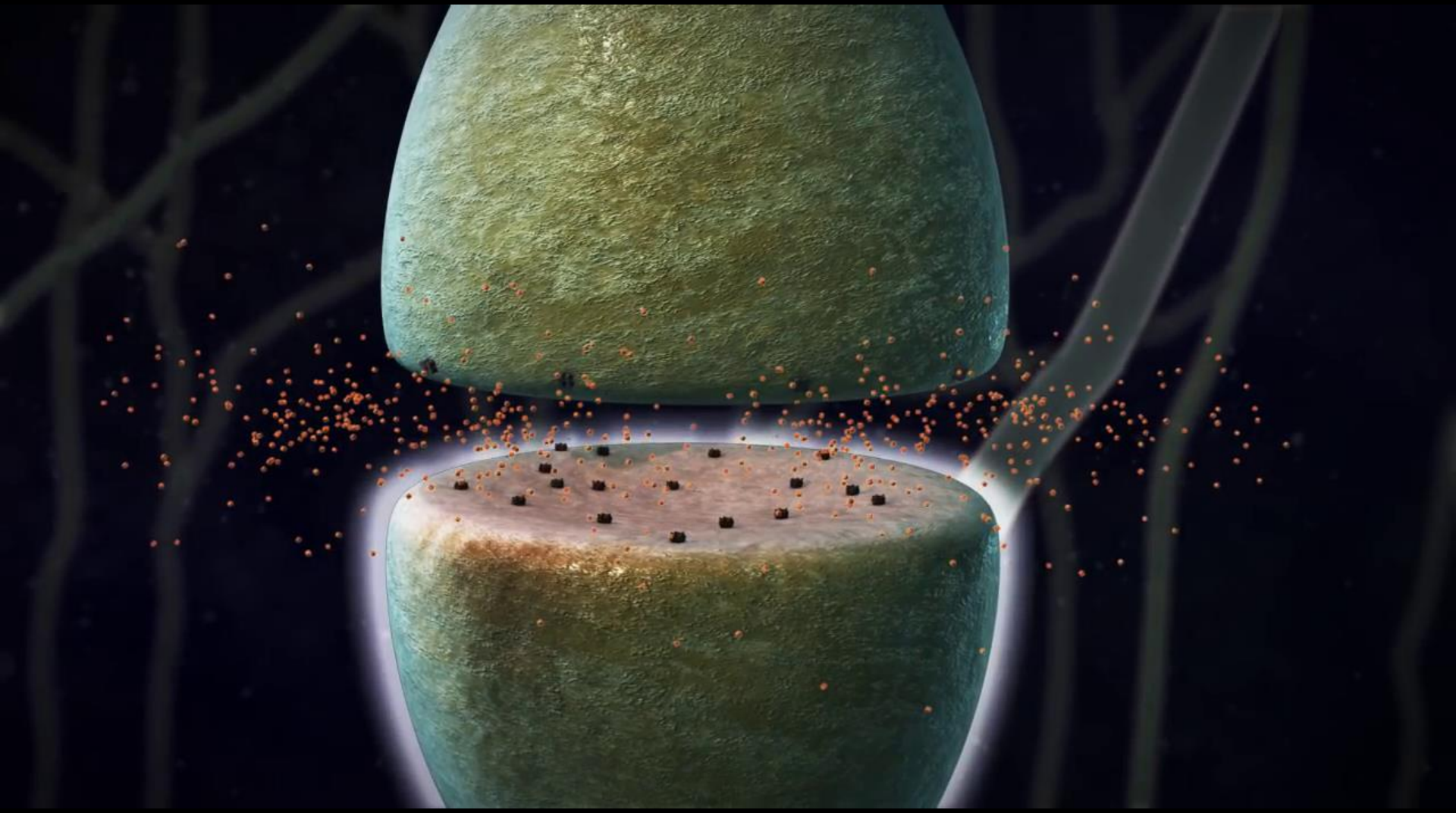


A **neuron** is an electrically excitable cell that processes & transmits information through electrical and chemical signals

Synapse


Synapse
Neurotransmitter
Receptor
Axon
Dendrite
Mitochondria



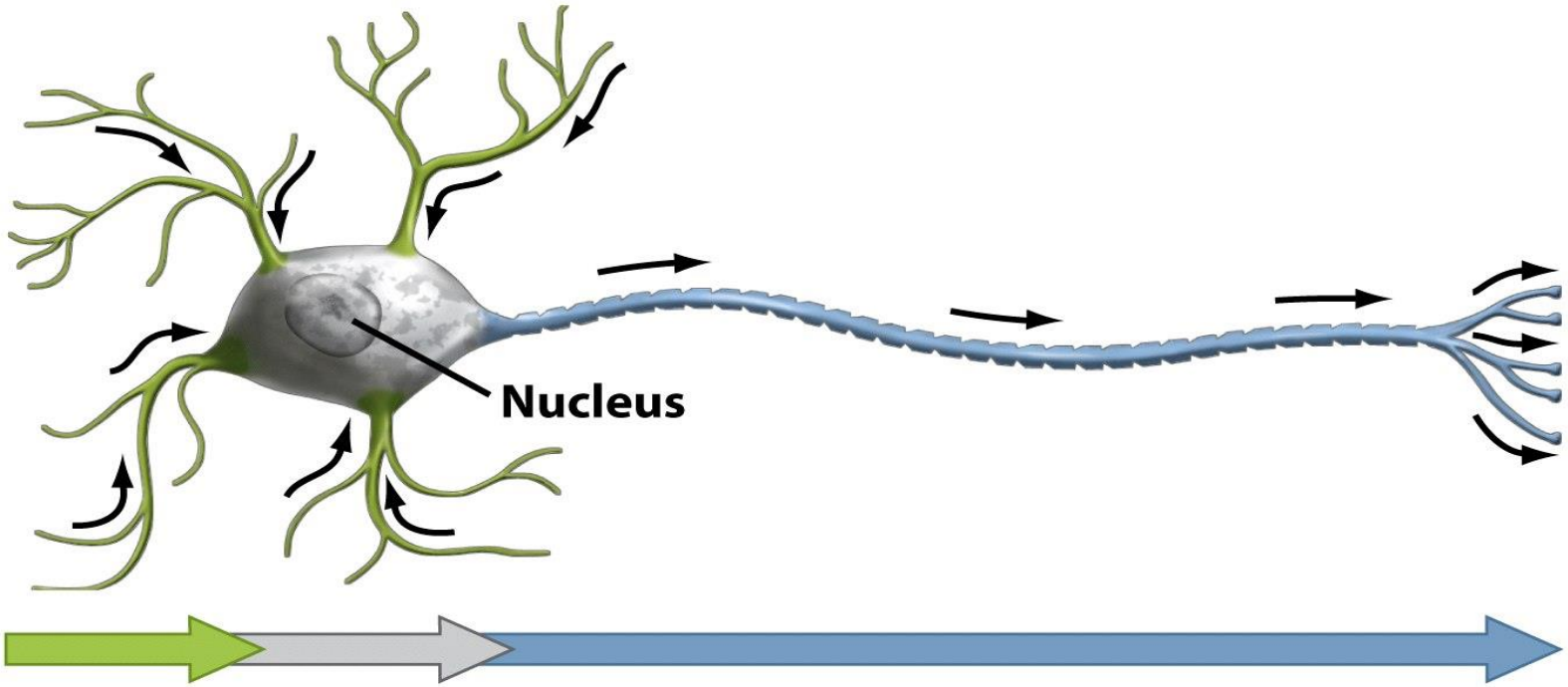


Signal transmission

Through Neuron: Impulse (Action potential)

From one Neuron to other: Neurotransmitter

Information flow through neurons

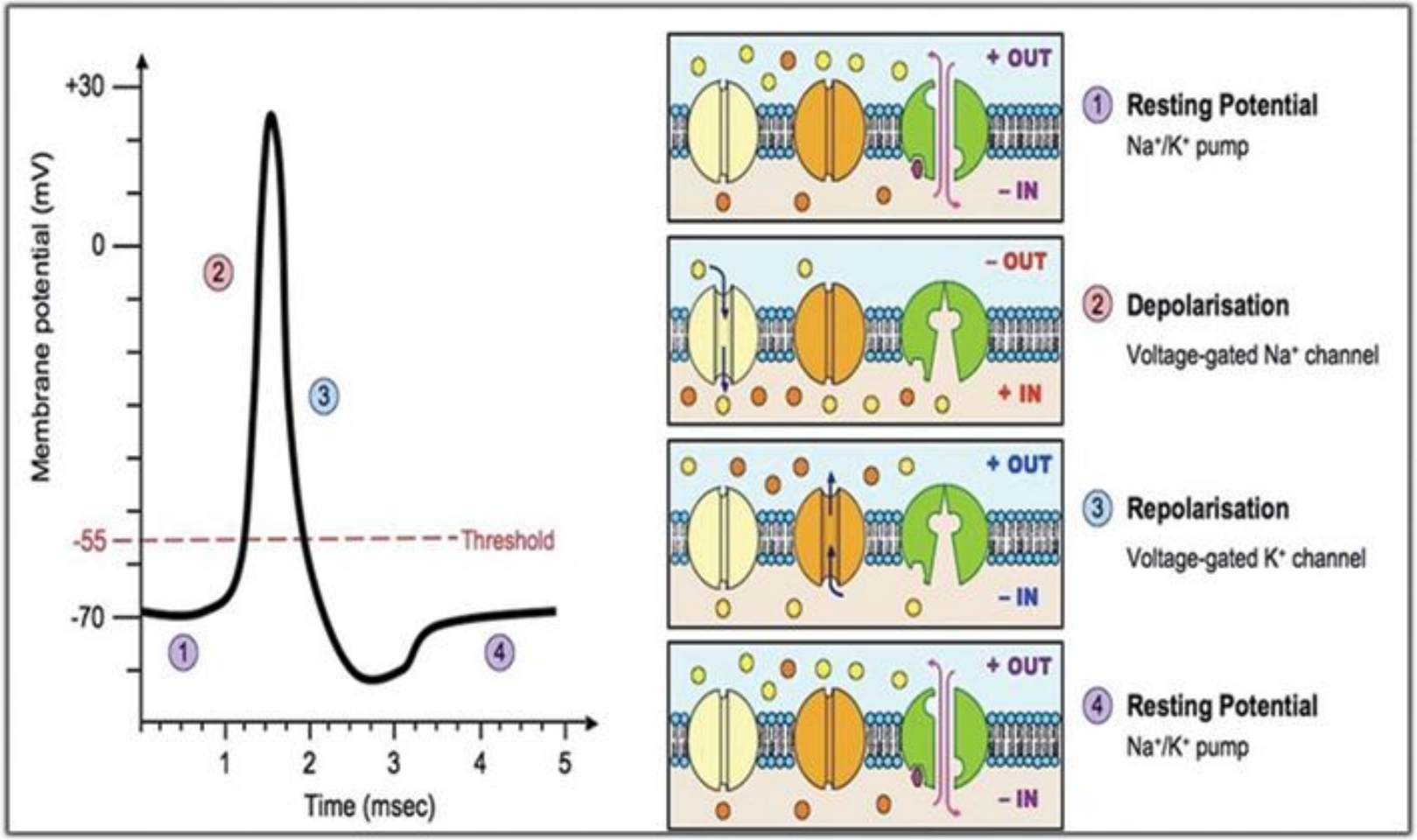


Dendrites
Collect electrical signals

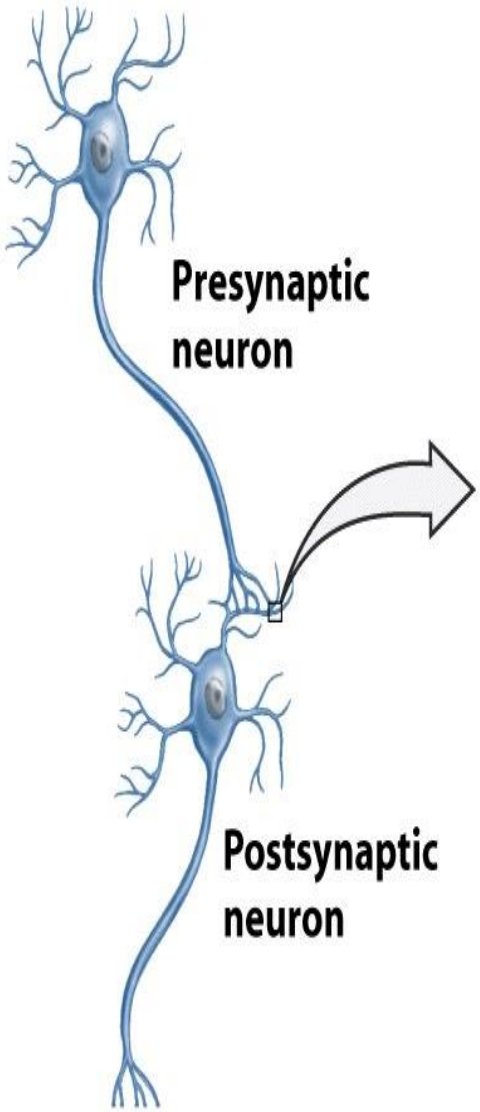
Cell body
Integrates incoming signals and generates outgoing signal to axon

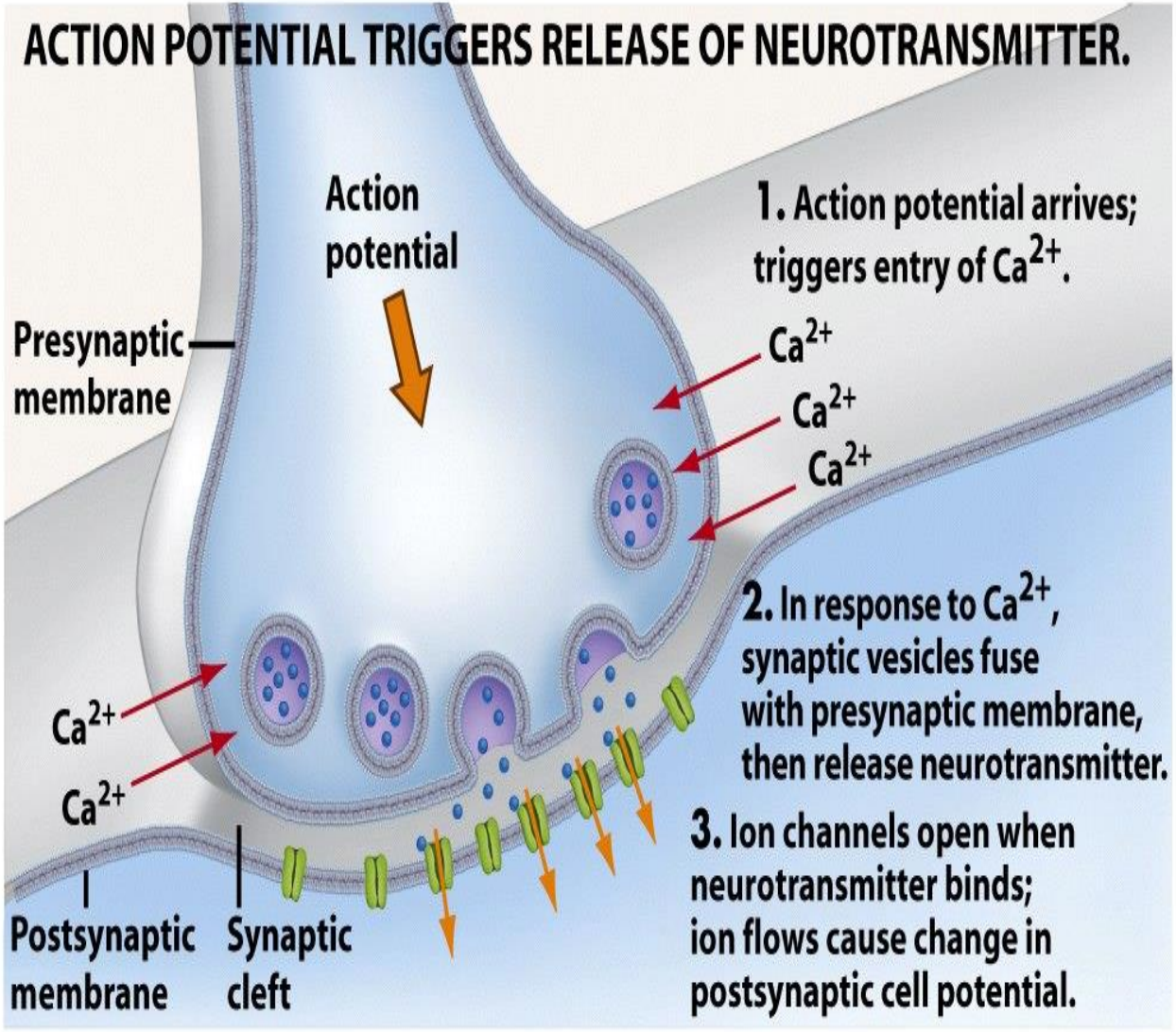
Axon
Passes electrical signals to dendrites of another cell or to an effector cell

Action potential



Signal transmission - Action Potential






AL MEDIA
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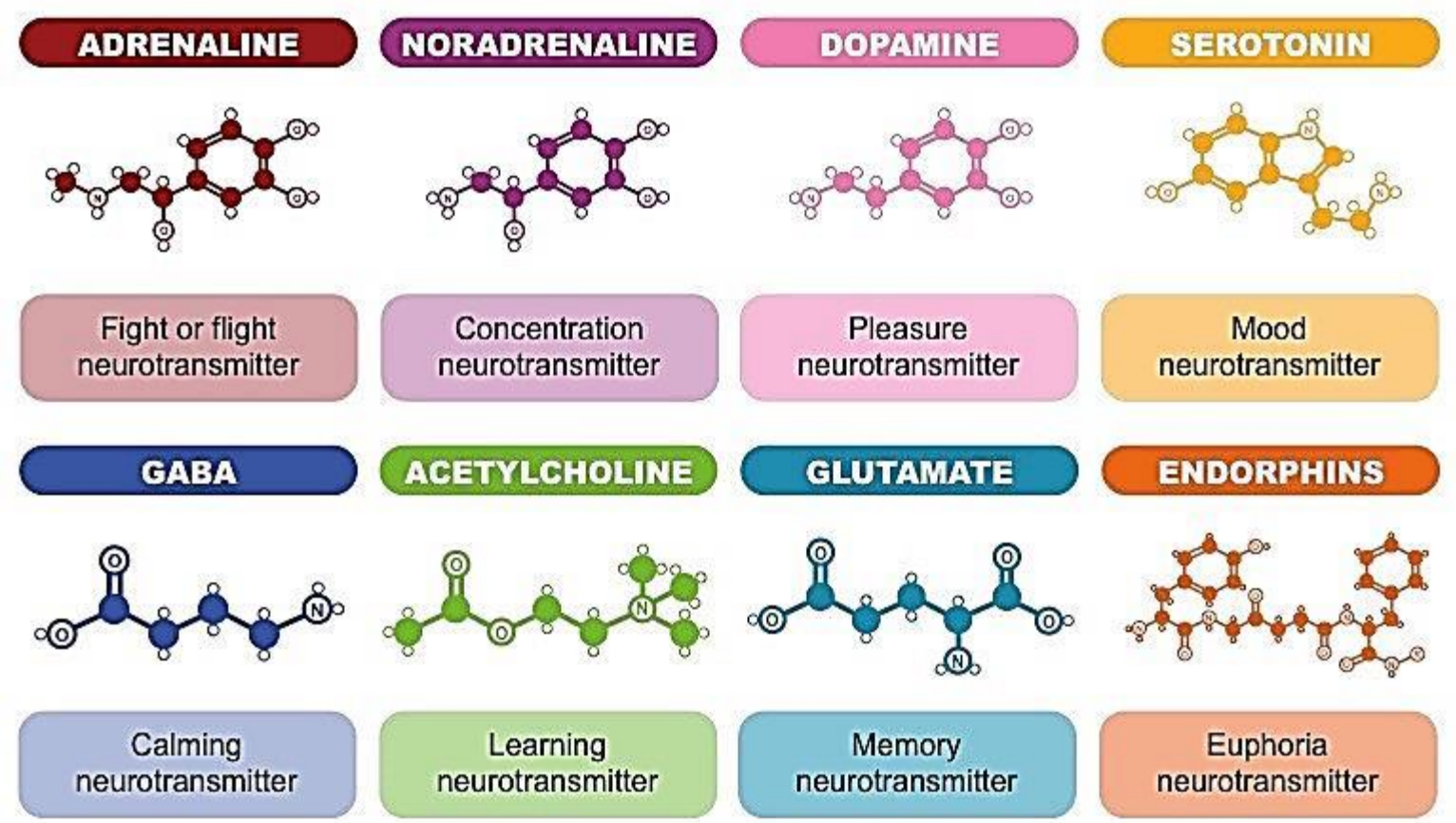
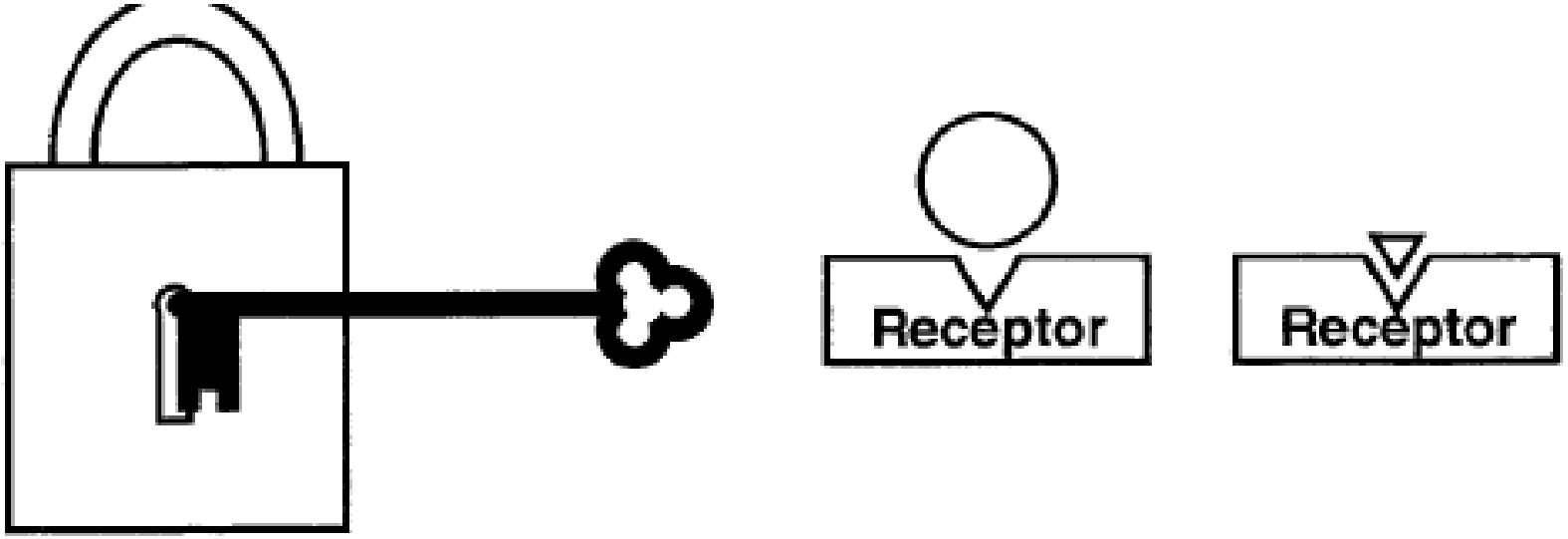
Neuro- Transmitters



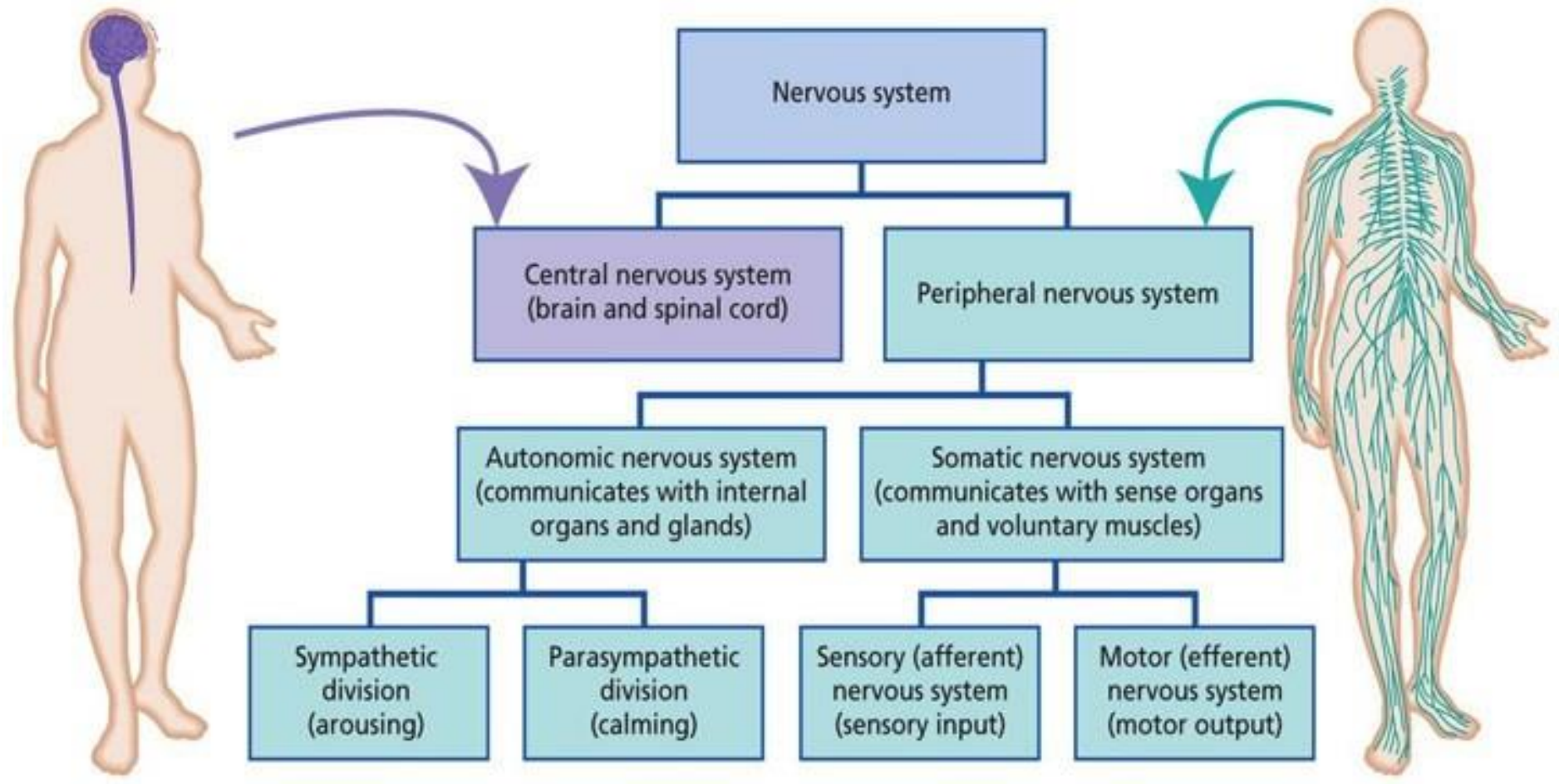
Neurotransmitters transmit signals across a synapse from one neuron to another

Receptors



A **receptor** is a protein-molecule that receives chemical-signals from outside a cell. When such chemical-signals bind to a **receptor**, they cause some form of cellular/tissue-response

Summary


Nervous system
Central nervous system (brain and spinal cord)
Peripheral nervous system
Autonomic nervous system (communicates with internal organs and glands)
Somatic nervous system (communicates with sense organs and voluntary muscles)
Sympathetic division (arousing)
Parasympathetic division (calming)
Sensory (afferent) nervous system (sensory input)
Motor (efferent) nervous system (motor output)

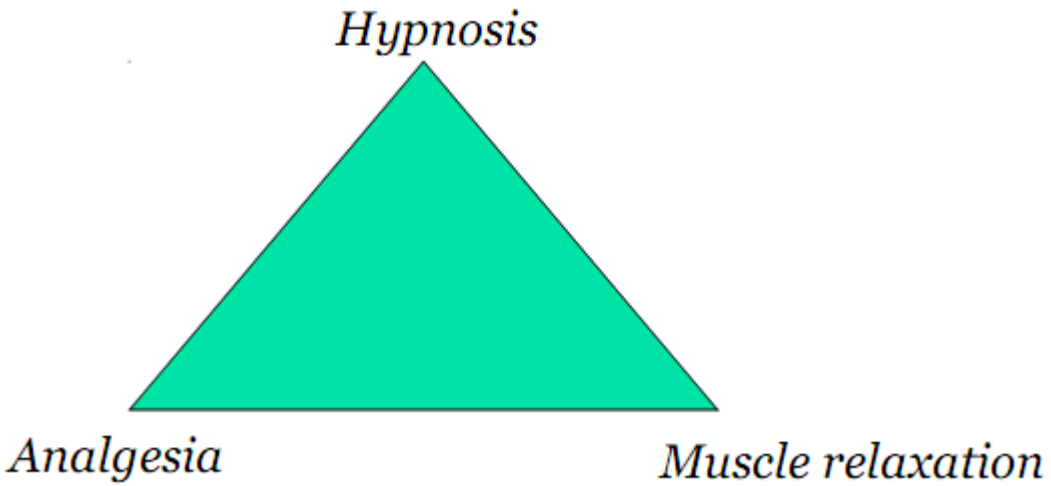
Thank You

ANAESTHESIA

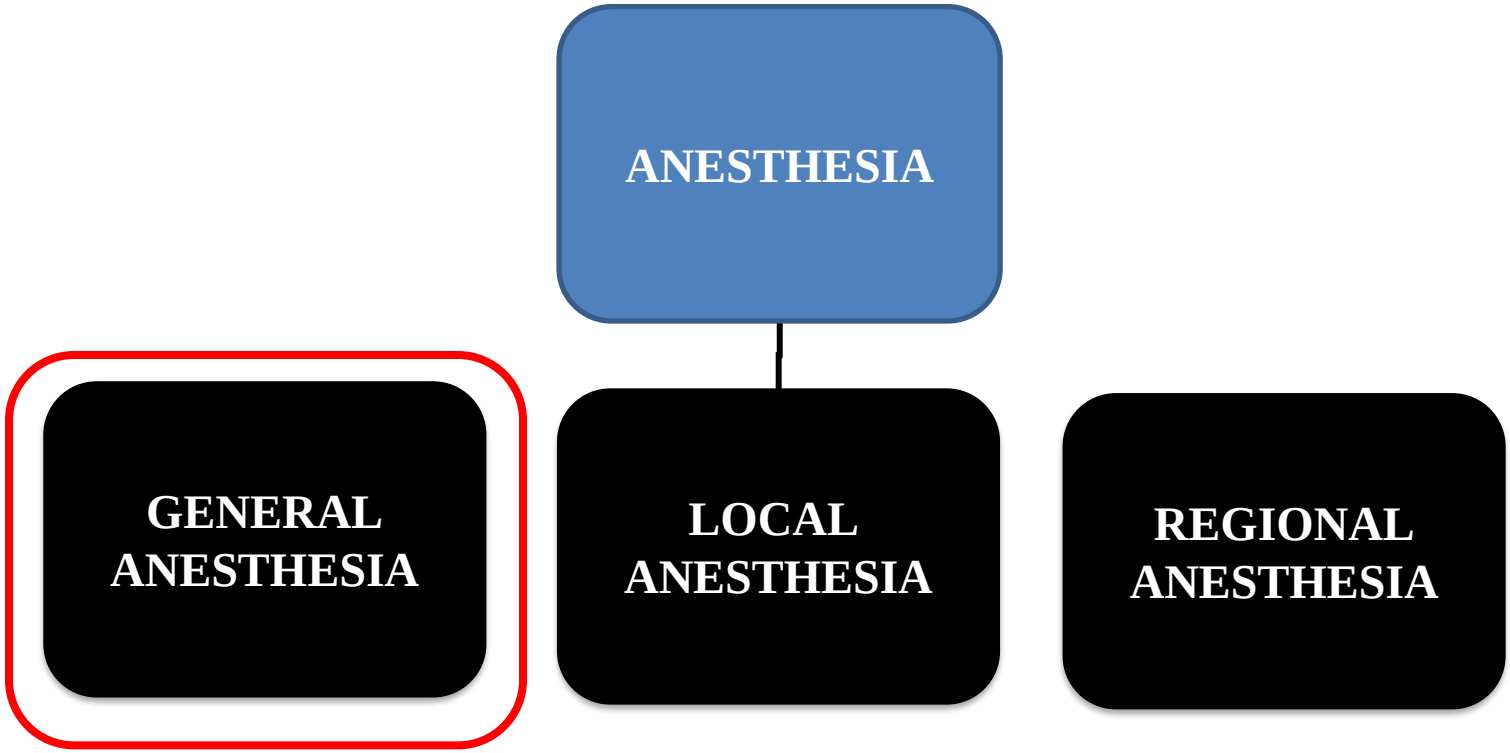
Anaesthesia

Anaesthesia means Blocking of perception of **pain** and other **sensations**

This allows patients to undergo **surgery** and other procedures without the suffering and pain they would otherwise experience



Types


ANESTHESIA
GENERAL ANESTHESIA
LOCAL ANESTHESIA
REGIONAL ANESTHESIA

General Anesthesia

All the protective reflexes are suppressed.

Amnesia (Inability to recall) is the main characteristic, while analgesia and muscle relaxation may be present, to varying degrees..

The medications used in general anesthesia are given by intravenously or by inhalation.

Stages Of General Anesthesia

Stage One: Analgesia.

The patient experiences analgesia or a loss of pain sensation but remains conscious & can carry on a conversation.

Stage Two: Excitement.

The patient may experience delirium (disturbed state of mind characterized by restlessness, illusions) or become violent.

B.P. rises & becomes irregular & breathing rate increases. This stage is typically bypassed by administering a barbiturate, such as sodium pentothal, before the anesthesia.

Stages Of General Anesthesia

Stage Three: Surgical Anesthesia.

During this stage, the skeletal muscles relax & the patient's breathing becomes regular. Eye movements slow, then stop & surgery can begin.

Stage Four: Medullary Paralysis.

This stage occurs if the respiratory centres in the medulla oblongata of the brain that control breathing & other vital functions cease to function.

Death can result if the patient cannot be revived quickly. This stage should never be reached. Careful control of the amounts of anesthetics administered prevent this occurrence.

Stages Of General Anesthesia

		Breathing	Eye movement	Pupil diameter	Eye reflexes	Muscle tone
Stage 1 Analgesia		Normal	Normal	Normal	Normal	Normal
Stage 2 Excitement		Increased variability	Decreasing	Dilated	Losing lid reflex	Increased involuntary movement
Stage 3 Surgical anaesthesia	**Plane 1**		Decreasing	Decreasing	Losing corneal reflex	Decreasing response to surgical stimulation
	Plane 2		Absent	Constricted	Losing light reflex	
	Plane 3		Absent	Normal		
	Plane 4		Absent	Dilated		
Stage 4 Imminent death		Apnoea	Absent	Maximally dilated	No reflexes	

MOA:

General anesthesia works by altering the flow of sodium molecules into nerve cells (neurons) through the cell membrane.

When the sodium molecules do not get into the neurons, nerve impulses are not generated and the brain becomes unconscious, does not store memories, does not register pain impulses from other areas of the body, and does not control involuntary reflexes.

I.V. Anesthetics

Intravenous injection works faster than inhalation. This minimizes the excitatory phase (Stage 2) and thus may reduce complications

- Dexmedetomidine
- Midazolam
- Ketamine
- Thiopental
- Opioids eg., Fentanyl, Morphine
- Propofol

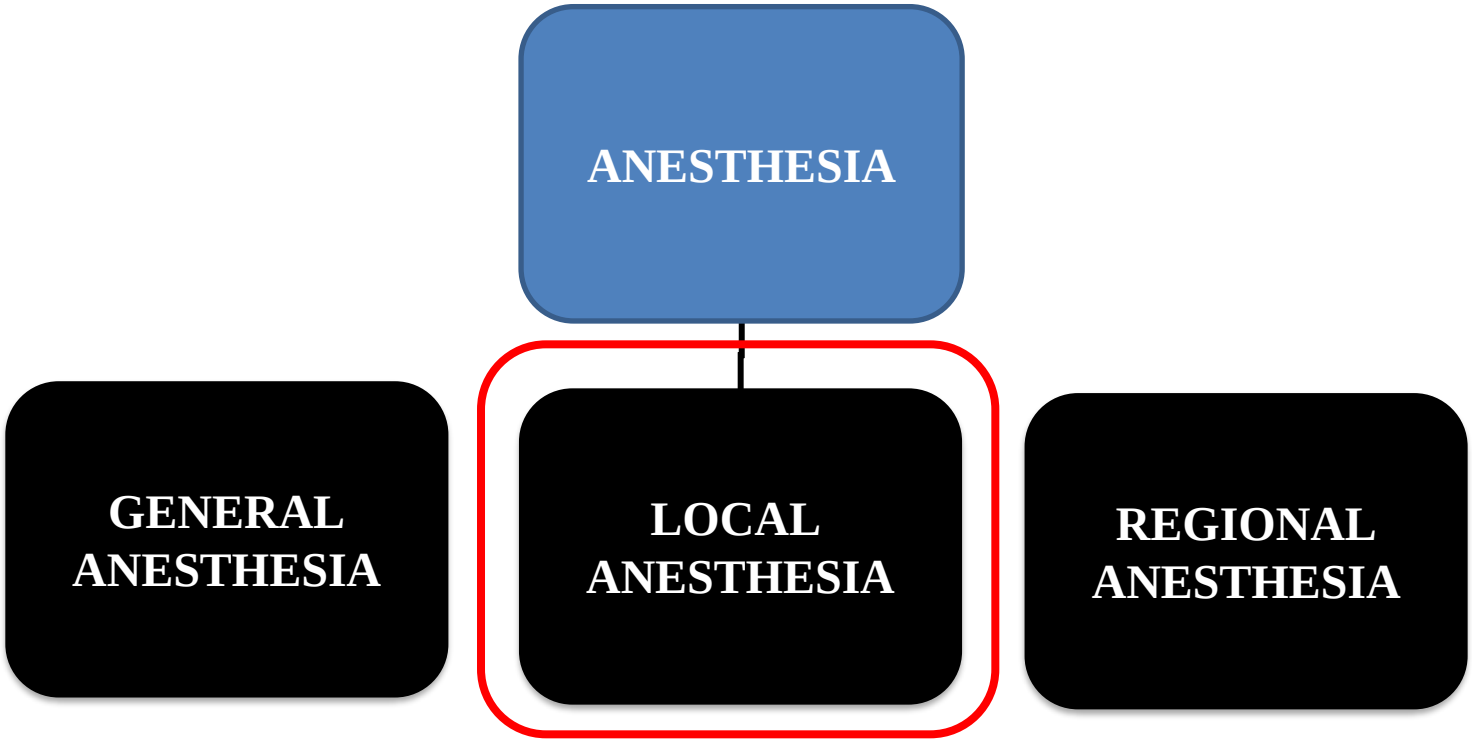
Inhalational General Anesthetics

Inhalational anaesthesia may be chosen when IV access is difficult to obtain (e.g., children), or when the patient prefers it.

- Halothane
- Enflurane
- Isoflurane
- Desfluorane
- Sevofluorane
- Nitrous oxide

- Video

Types


ANESTHESIA
GENERAL ANESTHESIA
LOCAL ANESTHESIA
REGIONAL ANESTHESIA

Local Anesthesia

It is used to block pain in a specific part of the body, allowing the patient to remain fully alert.

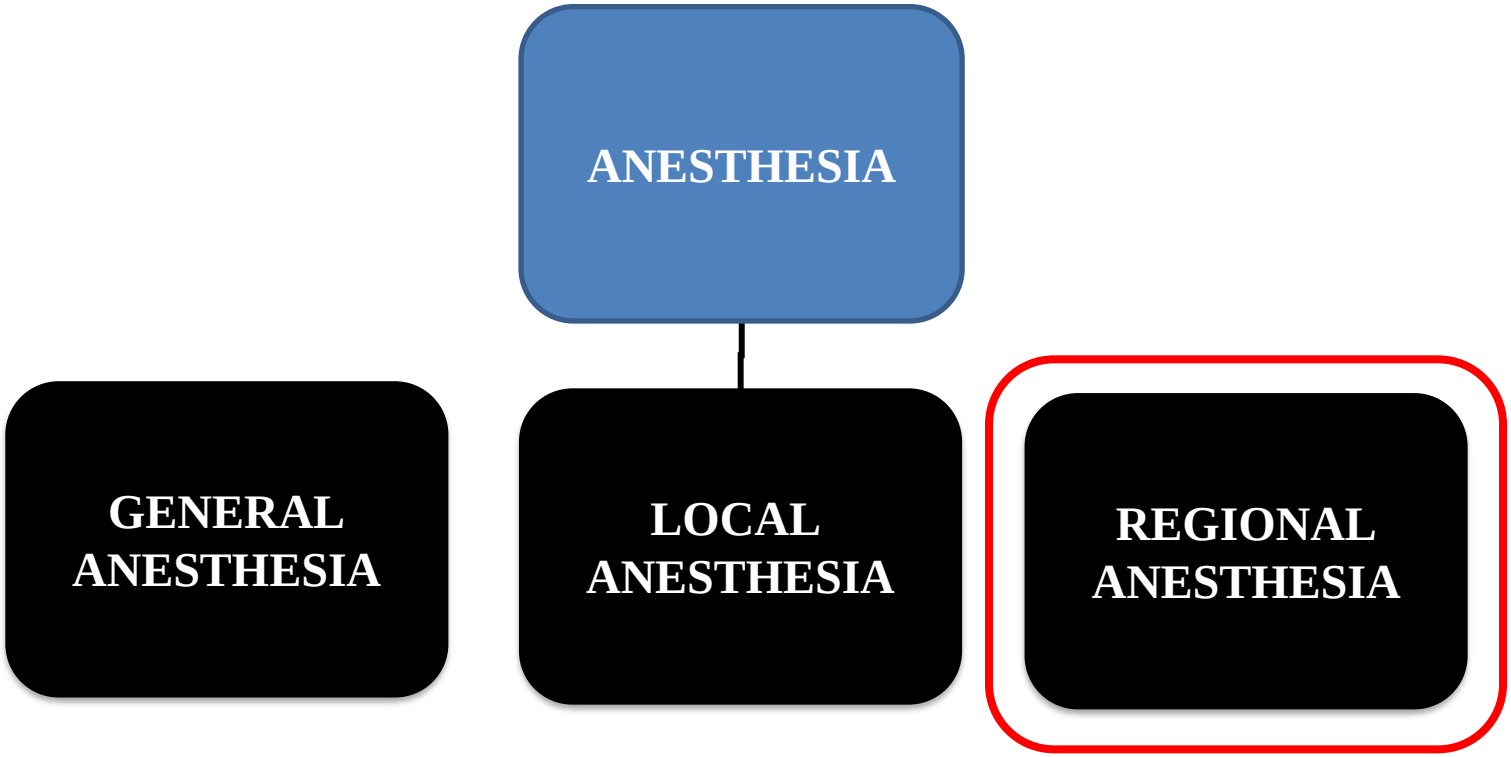
For local anesthesia, an anesthetic is injected at or near the site of the procedure.

Local anesthetics are generally for short duration of action.

Different types are: injections, sprays & ointments.

Example: - Lignocaine jelly and injection

Types


ANESTHESIA
GENERAL ANESTHESIA
LOCAL ANESTHESIA
REGIONAL ANESTHESIA

Regional Anesthesia

It is used to block sensation in a particular region of the body, such as, lower half of the body, eye, leg, etc.

The main advantage of regional anaesthesia is that it provides a high level of anaesthesia to a selected region of the body while having little effect on other areas.

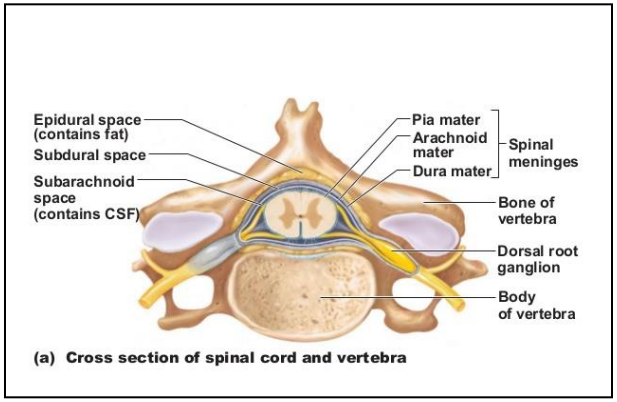
Regional Anesthetics

- Bupivacaine
- Levo- Bupivacaine
- Ropivacaine

Regional Anesthesia

Spinal Anesthesia

Refers to a regional block resulting from a small volume of anesthetic being injected into the **spinal canal**.



Epidural Anesthesia

Regional block resulting from an injection of a large volume of anesthetic into the **epidural space**. This is basically an injection around the spinal canal.

Spinal Anesthesia:

Refers to a regional block resulting from a small volume of local anesthetic being injected into the spinal canal.

The spinal canal is covered by the dura mater, through which the spinal needle enters.

Advantages Of Spinal Anesthesia

Patent airway: Control is not compromised, hence reduced risk of obstruction. This advantage may be lost with too much sedation.

Respiratory side effects: Less adverse effects.

Diabetic Patients: Such patients can return to their normal food and insulin regime soon after surgery.

Disadvantages Of Spinal Anesthesia

- It is difficult to locate Dural space
- Hypotension may occur with higher blocks
- Theoretical risk of introducing infection in sub arachnoid space causing meningitis

- Video of Spinal anaesthesia
- Video of Epidural anaesthesia

Drug Preferred by Anesthesiologist

Anesthesiologists use a wide variety of drugs, in multiple combinations, in order to ensure that patients remain comfortable, relaxed and free of pain during surgery or other procedures. Drugs administered by anesthesiologists are categorized as follows:

- **Local anesthetics:** Block transmission of nerve impulses without causing unconsciousness.
- **General anesthetics:** Bring about a state of unconsciousness.
- **Analgesics:** Relieve pain of patients before, during or after surgery.
- **Sedatives:** Bring about relaxation/calmness in a patient and reduce anxiety; higher doses can also be used to induce sleep.
- **Muscle Relaxants:** Work to paralyze skeletal muscles in order to facilitate intubation or surgery.

Major Challenge Anesthesiologist face

1. Airway Management
2. Hemodynamic Stability
3. Pain Management
4. Cardio Vascular Safety
5. Neurological safety
6. Renal Safety
7. Delirium Management
8. Nausea, Vomiting
9. Cost Saving
10. Medication Errors

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION
↓
5. MAINTENANCE
↓
6. RECOVERY
↓
7. POST OPERATIVE MANAGEMENT

1 Preparation In Anesthesia

- Discuss with the patient options for anesthesia.
- Explain risk and benefits
- What local anesthetic should be used?
- The addition of epinephrine may be considered to pr improve the quality of the block
- Choose an appropriate spinal needle.

  50 years and older patients: 22 gauge needle

  Less than 50 years of age: 25-27 gauge needle

  A smaller needle is used in the younger patient

- The patient should be inline to standard monitors including ECG, blood pressure, and pulse oximetry. Record an initial set of vital signs.
- Preload the patient with 1-1.5 liters of crystalloid intravenous solution

MONITORING

ECG - ElectroCardioGraphy
SpO2 - Blood saturation with O2
BP monitoring
Oxygen measurement
Capnography- Measures amount of CO2 exhaled by patient
Temperature measurement
Electroencephalography if needed

2 Premedication In Anesthesia

- Management of anesthesia begins with preoperative psychological preparation of the patient and administration of a drug or drugs selected to elicit specific pharmacological responses

- This initial psychological & pharmacologic component of anesthetics management is referred to as **"Premedication"**

- Pharmacological premedication is administration of drugs orally or Intramuscularly 1 to 2 hours before the anticipated induction of anesthesia

Example of drugs are used for premedication purpose:

Opioids, Benzodiazepine, Antihistamines, Alpha-2 agonists, Anticholinergics etc.

3

Intubation In Anesthesia:

- **Intubation, is the placement of a flexible polyvinyl chloride tube** (but specialty tubes constructed of silicone rubber, latex rubber, or stainless steel**) into the trachea (windpipe) to maintain an open airway or to serve as a conduit through which to administer certain drugs.**

- Most commonly used drugs include: Atracurium, Vecuronium, Rocuronium.

Endotracheal Intubation Video

4

Induction in Anesthesia:

- The administration of a drug or combination of drugs at the beginning of an anesthetics that results in a state of general anesthesia
- Most commonly used drugs are: Bupivacaine, Ropivacaine, Propofol etc

5

Maintenance of Anesthesia

- The next phase of anesthesia is called maintenance
- The Anaesthetist keeps a balance of medicines while carefully watching patient breathing, heart rate, blood pressure, and other vital functions
- Anesthesia is adjusted based on patient responses during the procedure
- Most commonly used drugs include:

  Antihypertensives drugs (To treat high BP)

  Ephedrine & phenylephrine (To treat low BP)

  Salbutamol (To treat asthma or laryngospasm/bronchospasm)

  Epinephrine or diphenhydramine (To treat allergic reactions)

6 Recovery In Anaesthesia (Emergence)

- This time is critical because it is a period of physiologic disturbance during which crisis can arise. Frequent observation and monitoring is required.

7 Post Operative Management

- The anaesthesia should conclude with a pain-free awakening and a management plan for postoperative pain relief.
- This may be in the form of regional analgesia, oral, transdermal or parenteral medication.
- Commonly used drugs include: Paracetamol, NSAID's, Ibuprofen, Opioids, Tramadol

Thank You

GENERAL ANAESTHESIA

General Anesthesia

Anesthesia : An = without ; aesthesis = no sensation

- The drugs which produces reversible loss of all sensation and consciousness

- Generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery

STAGES OF GENERAL ANAESTHESIA

Stage-1

- Analgesia: Start from beginning of anesthesia administration and last upto **loss of consciousness** feels a dream like state, reflexes and **respiration becomes normal.** This stage is usually described as the **"induction stage."**

Stage-2

- State of delirium: From **loss of consciousness to beginning of irregular respiration**. Apparent excitement is seen. Muscle tone increases. Jaws are tightly closed. Heart rate and blood pressure may rise.

Delirium: (disturbed state of mind characterized by restlessness, illusions)

Stat Pearls; Bilal A. Siddiqui; Anesthesia stages 2022 March

Stage-3

- Surgical anaesthesia: Extends from the **onset of irregular respiration to cessation of spontaneous breathing.** This has been divided into 4 planes
  - Plane 1: This plane ends when eyes become fixed
  - Plane 2: Loss of corneal and laryngeal reflexes
  - Plane 3: Pupil start dilating and light reflex
  - Plane 4: Dilated pupil, decrease muscle tone, BP falls
- This stage is defined as **maintenance of anaesthesia**

Stage-4

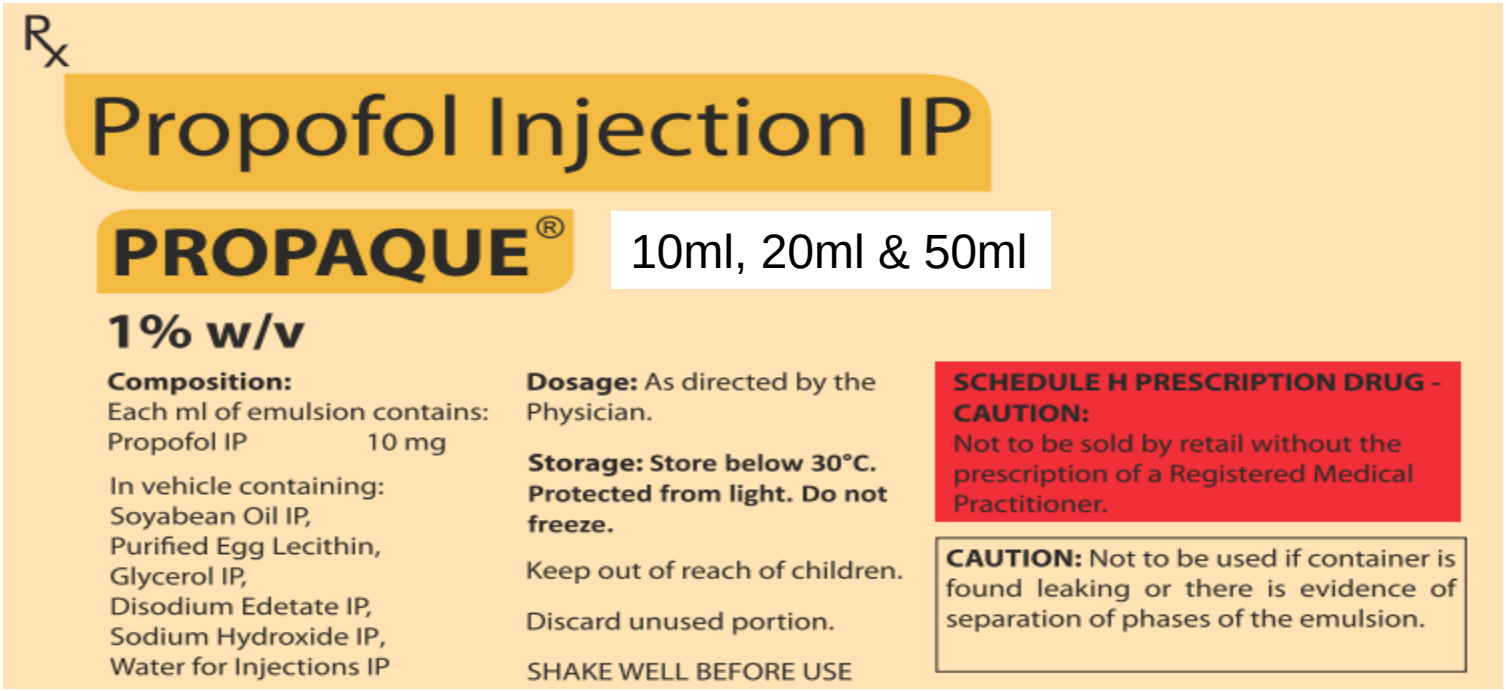
- Medullary paralysis: Respiratory and vasomotor control ceases

Stat Pearls; Bilal A. Siddiqui; Anesthesia stages 2022 March

DIFFERENCE BETWEEN GENERAL AND LOCAL ANAESTHETICS

	General anaesthesia	*Local anaesthesia*
1. Site of action	CNS	Peripheral nerves
2. Area of body involved	Whole body	Restricted area
3. Consciousness	Lost	Unaltered
4. Care of vital functions	Essential	Usually not needed
6. Poor health patient	Risky	Safer
7. Use in non-cooperative patient	Possible	Not possible
8. Major surgery	Preferred	Cannot be used
9. Minor surgery	Not preferred	Preferred

PROPOFOL


Rx
Propofol Injection IP
PROPAQUE®
10ml, 20ml & 50ml
1% w/v
Composition:
Each ml of emulsion contains:
Propofol IP 10 mg
In vehicle containing:
Soyabean Oil IP,
Purified Egg Lecithin,
Glycerol IP,
Disodium Edetate IP,
Sodium Hydroxide IP,
Water for Injections IP
Dosage: As directed by the Physician.
Storage: Store below 30°C. Protected from light. Do not freeze.
Keep out of reach of children.
Discard unused portion.
SHAKE WELL BEFORE USE
SCHEDULE H PRESCRIPTION DRUG - CAUTION:
Not to be sold by retail without the prescription of a Registered Medical Practitioner.
CAUTION: Not to be used if container is found leaking or there is evidence of separation of phases of the emulsion.

- Propofol is an intravenous anaesthetic agent used for **induction and maintenance of general anaesthesia**.

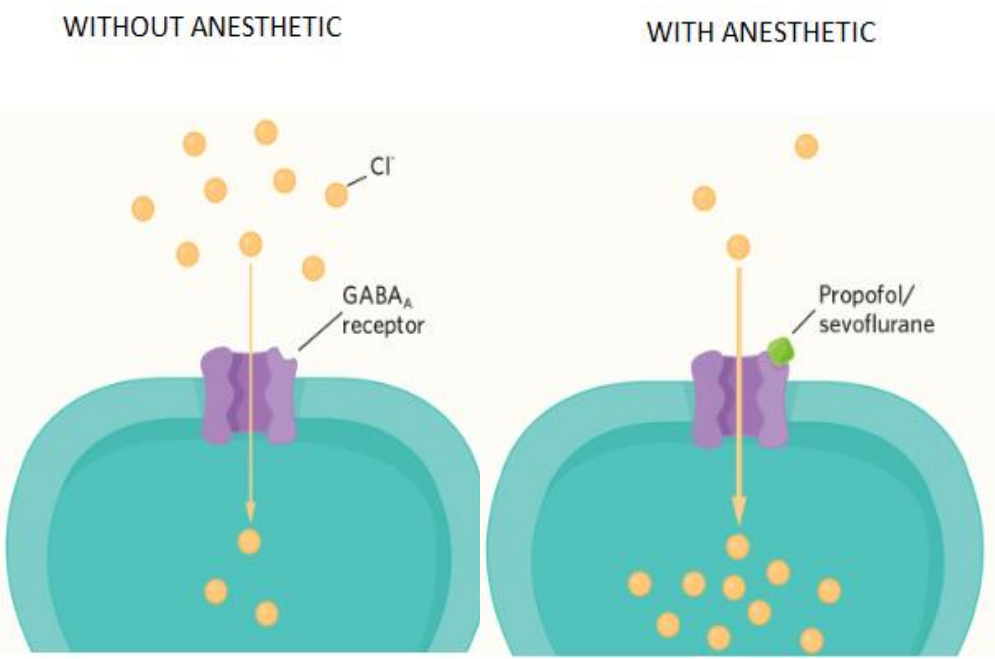
- Propofol is prepared in a **lipid emulsion which gives it the characteristic milky white appearance** and the colloquial name "**milk of amnesia.**"

Thomas B. Folino et al. StatPearls; Last Update May 8 2022

Mechanism of Action

MECHANISM OF ACTION

- The action of propofol involves a positive modulation of the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) through ligand gated GABA-A receptors.



Propofol

↓

Activation of GABA receptor

↓

Increase transmembrane Cl- conductance

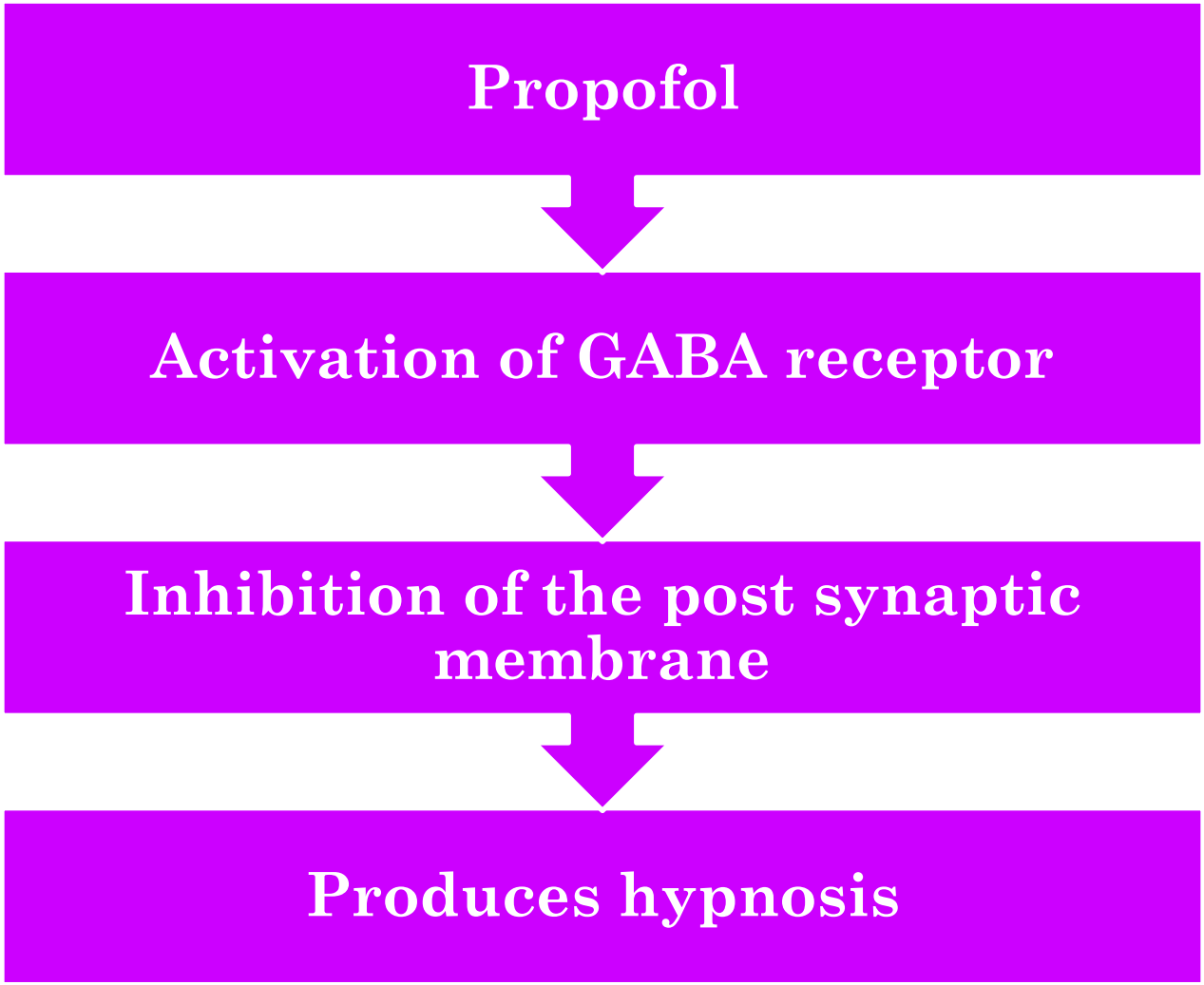
↓

Hyperpolarization of post synaptic membrane

↓

Functional inhibition of the post synaptic membrane

MECHANISM OF ACTION

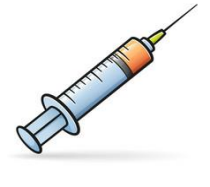


PHARMACODYNAMICS

- Propofol is a **sedative-hypnotic agent** for use in the induction and maintenance of anesthesia or sedation.

- Intravenous injection of a therapeutic dose of propofol **produces hypnosis rapidly with minimal excitation, usually within 40 seconds from the start of an injection** (the time for one arm-brain circulation).

PHARMACOKINETICS



Parameters	
Route of Administration	Intravenous
Onset of action	Propofol has a rapid onset of action that is dose-dependent and less than a minute.
Duration of action	An induction dose of propofol will have a clinical effect for approximately 10 minutes. The prolonged or repeated administration will accumulate in peripheral tissues and will cause an increased duration of action.

Thomas B. Folino et al. StatPearls; Last Update May 8 2022

INDICATION

Indication	Approved Patient Population
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only

DOSAGE AND ADMINISTRATION

Induction of Anesthesia:

Patient population	Dosage
Adult (less than 55 yrs):	**40 mg every 10 seconds until induction onset (2-2.5 mg/kg)**
Elderly, debilitated, hypovolumic or ASA grade III and above	20 mg every 10 seconds until induction onset (1-1.5 mg/kg)
Cardiac Anesthesia	20 mg every 10 seconds until induction onset (0.5-1.5 mg/kg)
Neurosurgical Patients	20 mg every 10 seconds until induction onset (1-2 mg/kg)
Pediatric Patients	healthy, from 3 -16 years of age: 2.5- 3.5 mg/kg administered over 20 -30 seconds.

- Propofol is not recommended before 3 yrs of age.

Maintenance Infusion:

Patient population	Dosage
In adult (55 yrs)	**100-200 mcg/kg/min (6-12 mg/kg/hr)**
Elderly, ASA grade III and above	50-100 mcg/kg/min (3 - 6 mg/kg/h)
Cardiac Anesthesia	Most patients require: Primary propofol with Secondary Opioid - 100 - 150 mcg/kg/min. Low-Dose propofol with Primary Opioid - 50 -100 mcg/kg/min).
Neurosurgical Patients:	100-200 mcg/kg/min (6-12 mg/kg/h).
Pediatric Patients - healthy, from 2 months of age to 16 years of age	125-300 mcg/kg/min (7.5 -18 mg/kg/h).

Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated

- **Adult Patients -** Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be **5 mcg/kg/min (0.3 mg/kg/h)** for at least 5 minutes.
- Subsequent increments of 5-10 mcg/kg/min (0.3-0.6 mg/kg/h) over 5-10 minutes may be used until desired clinical effect is achieved.
- Maintenance rates of 5-50 mcg/kg/min (0.3-3 mg/kg/h) or higher may be required. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks

Initiation of MAC Sedation

Patient population	Dosage
Healthy Adults Less Than 55 Years of Age	100-150 mcg/kg/min (6-9 mg/kg/h) for 3-5 minutes or a slow injection of 0.5 mg/kg over 3-5 minutes followed immediately by a maintenance infusion
Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients	Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided.

Maintenance of MAC Sedation

Patient population	Dosage
Healthy Adults Less Than 55 Years of Age	25-75 mcg/kg/min (1.5-4.5 mg/kg/h) or incremental bolus doses of 10-20 mg.
In Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients	Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used.

CONTRAINDICATION

- Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol or any of its components.

- Propofol injectable emulsion is contraindicated in patients with allergies to eggs, egg products, soyabeans or soya products.

OVERDOSAGE

- If overdosage occurs, Propofol administration should be discontinued immediately.

Overdosage is likely to cause cardiorespiratory depression.

- Respiratory depression should be treated by artificial ventilation with oxygen.
- Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents.

Clinical efficacy

1. INDUCTION OF GENERAL ANESTHESIA

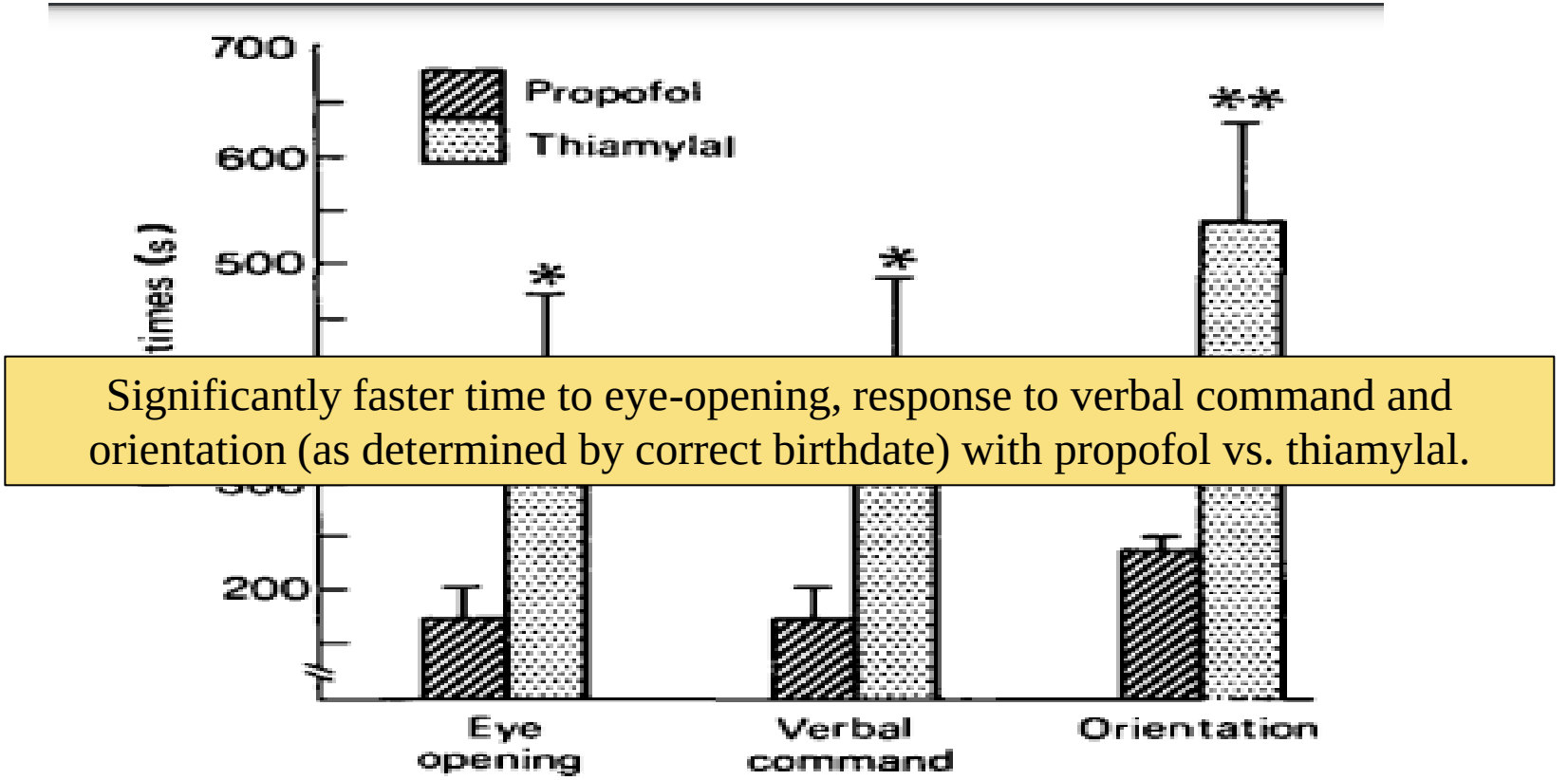
Rapid onset of action and recovery

- When a 2-2.5 mg/kg dose of propofol is administered over 20-30 seconds, **loss of consciousness occurs in 30-60 seconds**; this is similar to that reported following administration of equipotent doses of thiopental, etomidate, or methohexital.

- The **mean duration of the hypnotic effect after a single bolus dose of 2-2.5 mg/kg is approximately five minutes** and so may provide adequate anesthesia for procedures appropriate for this time frame.

DICp, The Annals of Pharmacotherapy 1989; October (23): 743-49

Recovery was rapid following propofol anaesthesia



Significantly faster time to eye-opening, response to verbal command and orientation (as determined by correct birthdate) with propofol vs. thiamylal.

Forty female patients, ASA class I or II, aged between 18 and 37 yr, were studied during elective termination of pregnancy on an outpatient basis. Propofol 2.5 mg /kg (n=19) or thiamylal 4.0 mg/kg (n=21)

Br.J. Anaesth. (1988), 61, 707-711

2. MAINTENANCE OF GENERAL ANESTHESIA

Acta Anaesthesiol Scand 1990: 34: 400–403

Randomized comparison of recovery after propofol-nitrous oxide versus thiopentone-isoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery

K. Korttila, P. Östman, E. Faure, J. L. Apfelbaum, J. Prunskis, M. Ekdawi and M. F. Roizen
Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois, USA

- Patient profile: Unpremedicated patients (34 women, 7 men) with ASA physical status I or II.
- The patients were scheduled for gynaecological laparoscopies, hysteroscopies, laser surgery, or other ambulatory surgical procedures.
- Propofol 2 mg/kg (n=18F/3M) or thiopentone 4 mg/kg (n=16F/4M) IV over a period of 30 s
- Anaesthesia was maintained with either propofol infusion or isoflurane (0.5-2y0), both with nitrous oxide (N,O) 66% and oxygen started 60 s after intubation.

Propofol infusion is preferable to thiopentone & isoflurane anaesthesia

Recovery after propofol or thiopentone-isoflurane anaesthesia (mean ± s.d.)

N_2O off to:	Propofol	Thiopentone-isoflurane
Extubation (min)	3.8 ± 2.7	4.7 ± 3.2
PARS 10 (min)	23 ± 26	23 ± 14
Able to sit (min)	58 ± 23	77 ± 35
"Home-ready" (min)	136 ± 77*	204 ± 101
Tapping board	104 ± 38	129 ± 55
Maddox wing	112 ± 42	140 ± 50

*$P < 0.05$ propofol vs thiopentone-isoflurane.

Early recovery times were significantly shorter in the propofol group vs. isoflurane group

Significantly faster Intermediate recovery times in propofol group than in the isoflurane group.

Patients in the propofol group were "home-ready" significantly faster than patients in the isoflurane group

Acta Anaesthesiol Scand 1990: 34: 400-403

Significantly less emesis was observed in propofol group vs.isoflurane group in the PACU

Emesis after propofol or isoflurane anesthesia in the PACU.

	Propofol	Thiopentone-isoflurane
None	12*	5
Emesis overall	7	15
Nausea	7	6
Retching	0	1
Vomiting	0	8

*$P < 0.05$ vs thiopentone-isoflurane.

Post anaesthesia care unit (PACU)

Acta Anaesthesiol Scand 1990: 34: 400-403

3. ICU SEDATION OF INTUBATED, MECHANICALLY VENTILATED PATIENTS

ADIS DRUG EVALUATION

CNS Drugs 2003; 17 (4): 235-272
1172-7047/03/0004-0235/$30.00/0

Propofol

A Review of its Use in Intensive Care Sedation of Adults

Kate McKeage and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Short- (≤24 Hours) and Medium-Term (24–72 Hours) Sedation

Reference	Patient type	Drug and no. of patients enrolled	Mean dosage (mg/kg/h)	Mean duration of infusion (h)	Results: time with adequate or ideal sedation (%)	Results: mean time to recovery (min)[a]
Comparisons with MID						
Short- (≤24h) and medium-term (24–72h) sedation						
Aitkenhead et al.	Gen surg, med, trauma	PRO 53	1.77	20.2	94[b]	5**[c]
		MID 47	0.10	21.3	93[b]	148[d]
Beyer & Seyde	Abd surg	PRO 20[e]	1.9	24		14*
						3*
						8
		MID 20	0.17	11.9		150
Fruh	Gen surg, med, trauma	PRO 10	1.62	10		13.8[h]
		MID 10	0.2	10		35.3
Hall et al.	Gen surg, med, trauma	PRO 21				336*
		MID 26				714

Significantly shorter recovery time with propofol vs. midazolam

b Ramsay score 2–4;
c 21 evaluable patients;
d 18 evaluable patients.
e Total number of patients; distribution not specified.
abd surg = abdominal surgery; gen surg = general surgery; med = medical; MID = midazolam

CNS Drugs 2003;17(4): 235-72

Long-Term (>72 hours) Sedation

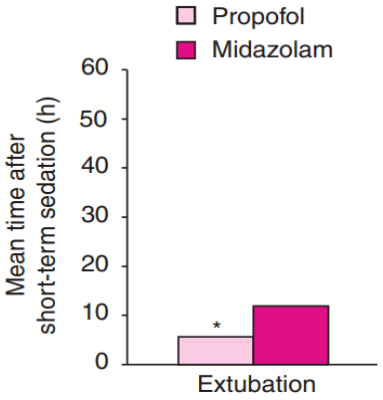
Reference	Patient type	Drug and no. of patients enrolled	Mean dosage (mg/kg/h)	Mean duration of infusion (h)	Results	
					time with adequate or ideal sedation (%)	mean time to recovery (min)[a]
Long-term sedation (>72h)						
Barrientos-Vega et al.[9]	Gen surg, med, trauma	PRO 54		139.7	67[i]	2 088[**j]
		MID 54		141.7	57[i]	5 874[k]
Carrasco et al.[41]	Gen surg, med, trauma	PRO 16	2.2	116.4		24*
C						
C						
Hall et al.[64]	Gen surg, med, trauma	PRO 4				504*
		MID 10				2 808
Weinbroum et al.[14]	Gen surg, med, trauma	PRO 31	1.8	99		108*
		MID 36	0.07	141		168

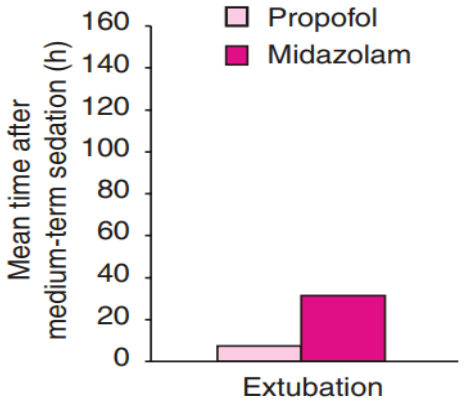
Improvement in time to recovery and extubation with propofol vs. midazolam

i Administered as bolus dosages.
abd surg = abdominal surgery; gen surg = general surgery; med = medical; MID = midazolam

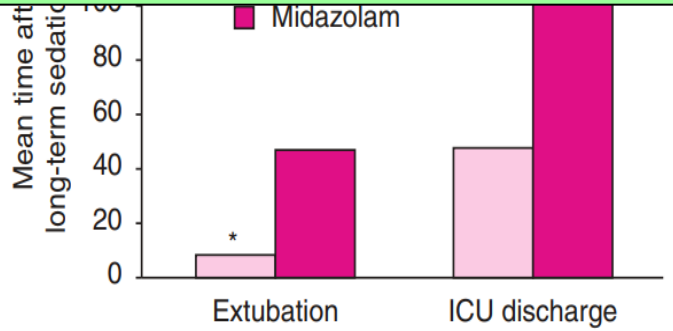
CNS Drugs 2003;17(4): 235-72

Comparisons of Short-, Medium- and Long-Term Sedation





Significantly shorter time to tracheal extubation with propofol vs. midazolam in the short- and long-term sedation sub groups.



N= Critically ill patients requiring continuous sedation while receiving mechanical ventilation. Propofol infusion of 0.3 to 0.6 mg/kg/h initially, which was subsequently titrated to achieve a target Ramsay sedation score (n=21) vs. Midazolam infusion of 0.012 to 0.024 mg/kg/h adjusted to achieve the target Ramsay sedation score (n=26)

Chest 2001 Apr; 119 (4): 1151-9

4. COMBINED SEDATION AND REGIONAL ANESTHESIA

Propofol is the nearest to an ideal agent for sedation during regional anaesthesia, **because of is pharmacokinetic profile, with rapid onset and offset.**

Br J Anaesth 2008; 100: 8–16

5. INITIATION AND MAINTENANCE OF MAC (MONITERED ANESTHESIA CARE) SEDATION

A Comparative Evaluation of Propofol and Midazolam as Sedative Agents in Fiberoptic Bronchoscopy*

Kevin Clarkson, M.B.; Camillus K. Power, M.B.; Finbar O'Connell, M.B.; Shri Pathmakanthan, M.B.; and Conor M. Burke, M.D., F.C.C.P.

Patient Profile

- Forty-one consecutive patients with known bronchial asthma (American Thoracic Society criteria) undergoing elective fiberoptic bronchoscopy were randomly allocated to receive either intravenous
- Midazolam (n=20) or propofol (n=21) as a sedative agent.

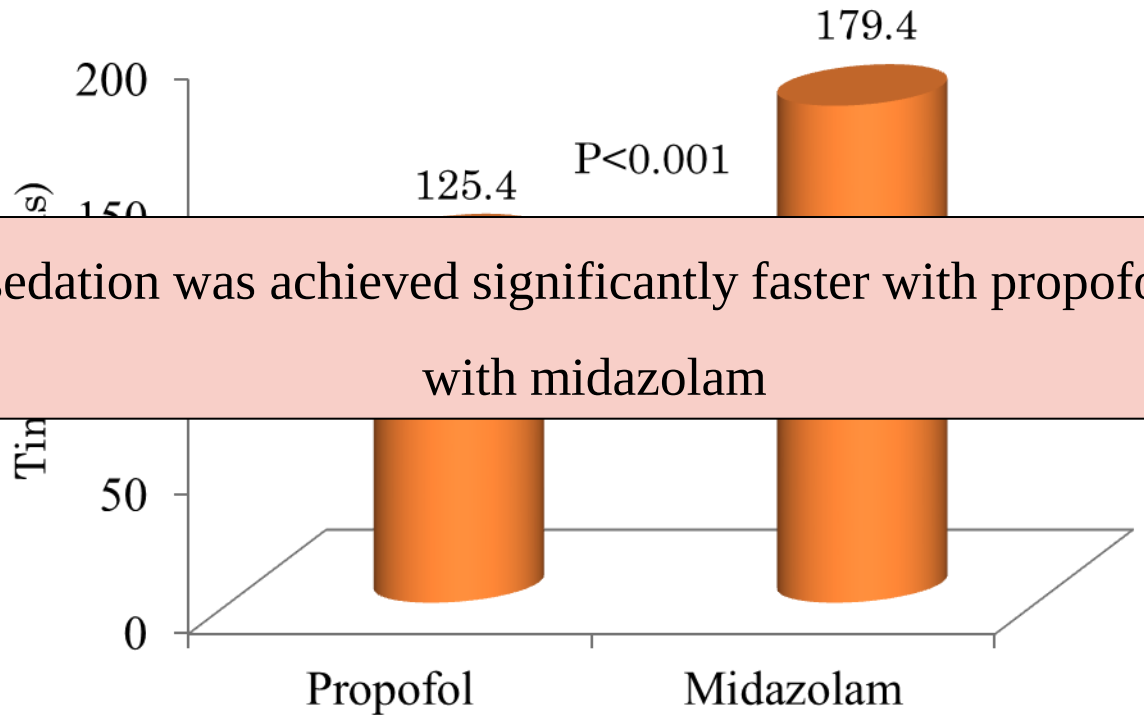
Dosage

- The patients in the midazolam group initially received 2 mg IV over 30 s. The patients in the propofol group received an initial IV infusion of 60 to 80 mg/min up to 2.0 mg/kg until adequate sedation was achieved.

Fiberoptic bronchoscopy: It is an invasive procedure that has been used for diagnostic and therapeutic purposes.

Chest 1993 Oct;104(4):1029-31

Propofol is a useful sedating agent with faster onset of action.



Level of sedation was achieved significantly faster with propofol compared with midazolam

Chest 1993 Oct;104(4):1029-31

FORMUALTION

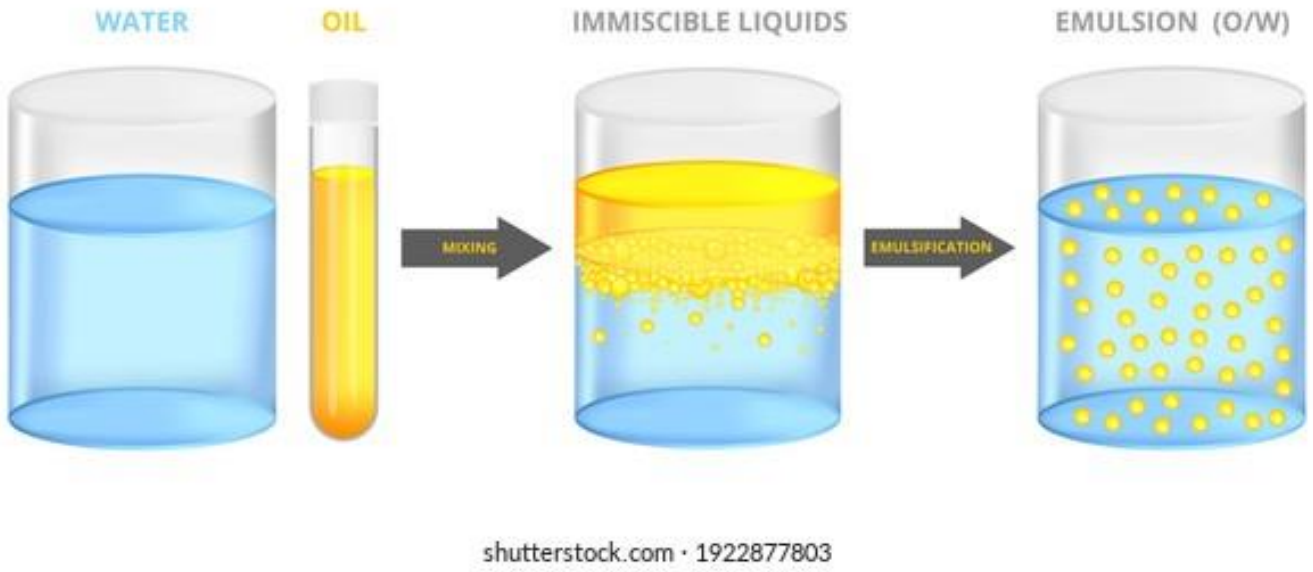
Propofol LCT

INTRODUCTION

- Propofol is an oil-in-water or lipid-based emulsion
- It is highly lipophilic
- This means that propofol miscibility can only be achieved in lipophilic substances or organic solvents
- This is achieved by emulsifiers, that facilitate dispersion of the drug molecule within the aqueous phase

EMULSION

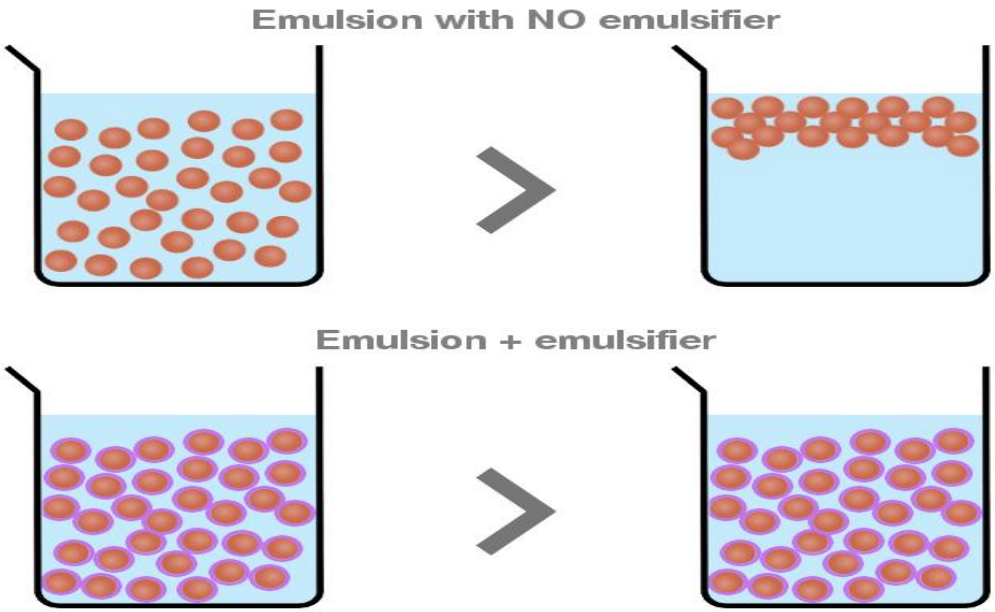
- An emulsion is a mixture of two or more liquids that are normally immiscible (unmixable or unblendable)



EMULSIFIER

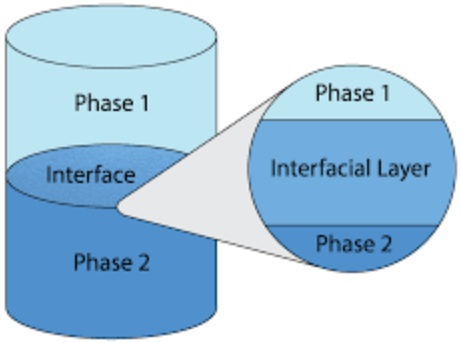
- An emulsifier is an additive which helps two liquids mix.

- Emulsifier used in propofol
  - Soyabean oil and lecithin



Effect of emulsion on drug absorption

- Total interfacial surface area is a highly important factor in the rate of drug release from a drug containing droplet in an emulsion (emulsion slows the availability of free drug)



This in turn is dependent on the size and number of oil droplets

More the no of droplets and smaller their size - Better is the absorption

What should be the Emulsion Droplet Size?

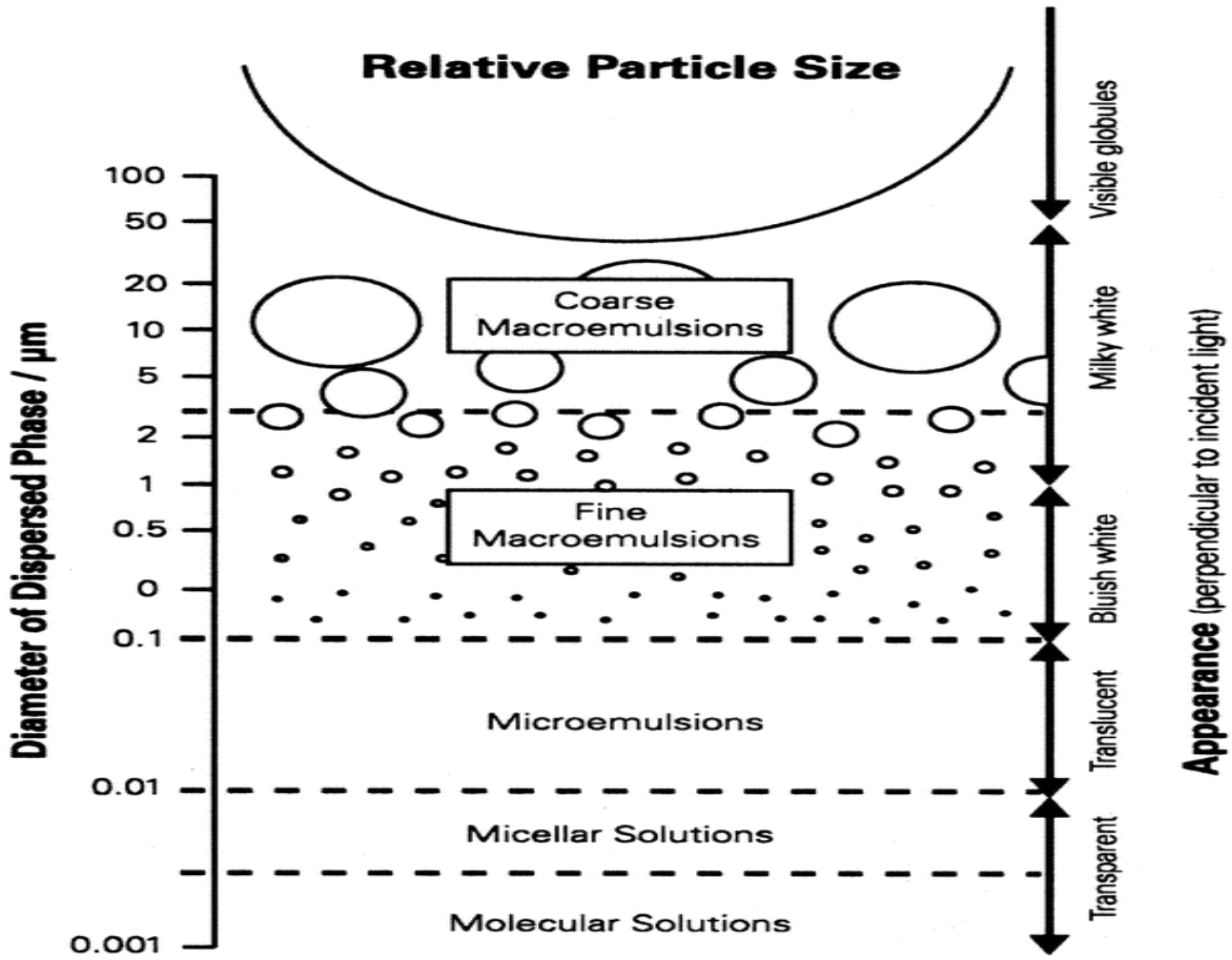
- It should be **sufficiently small** so that they can **pass through capillaries** (5–7 µm) without causing emboli.

- **Optimal size is generally considered <1 µm (1 µm = 1000 nm)**

- **Propofol emulsion and other emulsions** for intravenous delivery are manufactured so that the **oil droplets average 0.10– 0.3 µm** (100–300 nm).

Anesthesiology. 2005;103(4):860-876.

Relation of particle size to visual appearance of particle-containing dispersions



Anesthesiology. 2005;103(4):860-876.

Pain on injection with propofol

- Propofol is a membrane irritant
- Three out of five patients experience pain on injection of propofol, with one of these patients reporting severe or excruciating pain[1]
- About 60% of patients experience pain on injection with standard propofol alone—that is, without any preventive measures
- Pain on injection has been linked to the free propofol drug concentration[2]

1. *BMJ 2011; 342: d1110*
2. *Sim JY, et al. Br J Clin Pharmacol 2009; 67: 316-325*

INTERVENTIONS FOR REDUCING PAIN

- Propofol injection in antecubital vein
- ***Lidocaine pretreatment with venous occlusion***
- Opioid pretreatment
- Ketamine pretreatment
- NSAID pretreatment

Comparison of propofol emulsions with LCT and MCT/LCT

Propofol composition: Differences between LCT only and MCT/LCT

Sr No	Propofol LCT	Propofol MCT/LCT	Use
1.	Propofol	Propofol	Active drug
2	Soybean oil, Egg Lecithin (LCTs)	Soya oil, Egg lecithin, oleic acid (LCTs)	Emulsifier
3	-	Medium chain triglycerides	Emulsifier
4	Disodium EDTA dihydrate	-	Antimicrobial & preservative
5	Glycerin	Glycerol	Antimicrobial & preservative
6	NaOH	NaOH	To adjust pH
7	Nitrogen gas	-	To adjust pH
8	Water for injection	Water for injections	

LIDOCAINE PRETREATMENT WITH VENOUS OCCLUSION

- **Pretreatment using lidocaine** in conjunction with venous occlusion is one of the interventions to reduce pain on injection with propofol

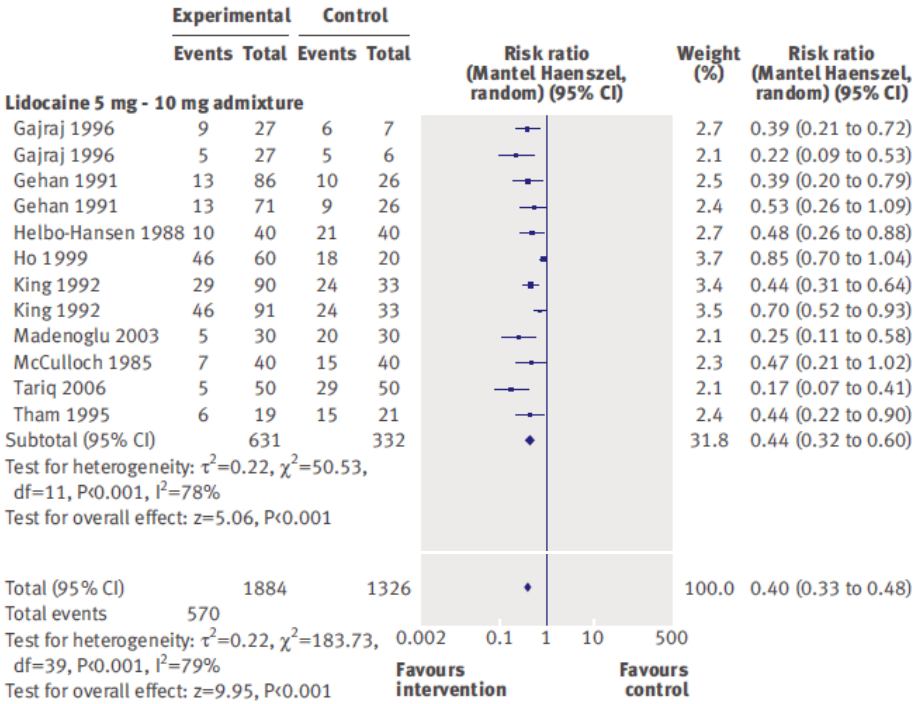


Fig 3 | Risk of pain on injection of lidocaine-propofol admixture

Lidocaine is always used with propofol to prevent pain at injection site

BMJ 2011;342:d1110

RESEARCH ARTICLE

Comparing the Injection Pain of Propofol Emulsion 1% (MCT/LCT) and Propofol Emulsion 2% (Propofol Lipuro) in Combination with Lidocaine in Patients Undergoing Gynecologic Surgery with General Anesthesia

Anahita Hirmanpour[1], Reihanak Talakoub[1], Mohammadreza Safavi[1]*, Azim Honarmand[1], Amir Shafa[1], Kamelia Emamdoost[1]

- Interventions
  - Group 1: propofol 1% (MCT/LCT) + lidocaine
  - Group 2: Propofol 1% (MCT/LCT) + distilled water.
  - Group 3: Propofol 2% (MCT) + lidocaine
  - Group 4: Propofol 2% (MCT) + distilled water

Results: Highest pain scores were found in the propofol 1% (MCT/LCT, Fresenius cabi) without lidocaine use while lipuropropofol (MCT, propofolLipuro, B-BRAUN) plus lidocaine had the lowest pain scores.

Pain is always high in propofol administered without lidocaine

Archives of Anesthesiology and Critical Care (Summer 2017); 3 (3): 342-347

Comparison of propofol emulsions with LCT and MCT/LCT

	1 % propofol emulsion with MCT/LCT	2 % propofol emulsion with MCT/LCT	1% propofol emulsion with LCT only
Effect on propofol PK	Similar (little) effects observed on propofol pharmacokinetics		
Formation of potentially toxic ketone bodies	Yes (acetoacetate and ß-hydroxybutyrate. Octanoate (8:0) liberated from such emulsions is potentially toxic[1]		No
Pain at injection site	Less pain than 1% propofol emulsion with LCT	Greater pain than 1% propofol emulsion with LCT only[2]	
Induction time	Not prolonged	Prolonged induction time than 1% propofol emulsion with LCT[2]	

Pain on injection has been linked to the free propofol drug concentration

1. Traul KA, et al. Food Chem Toxicol 2000; 38:79–98
2. Ward DS, et al. ANESTHESIOLOGY 2002; 97:1401–8

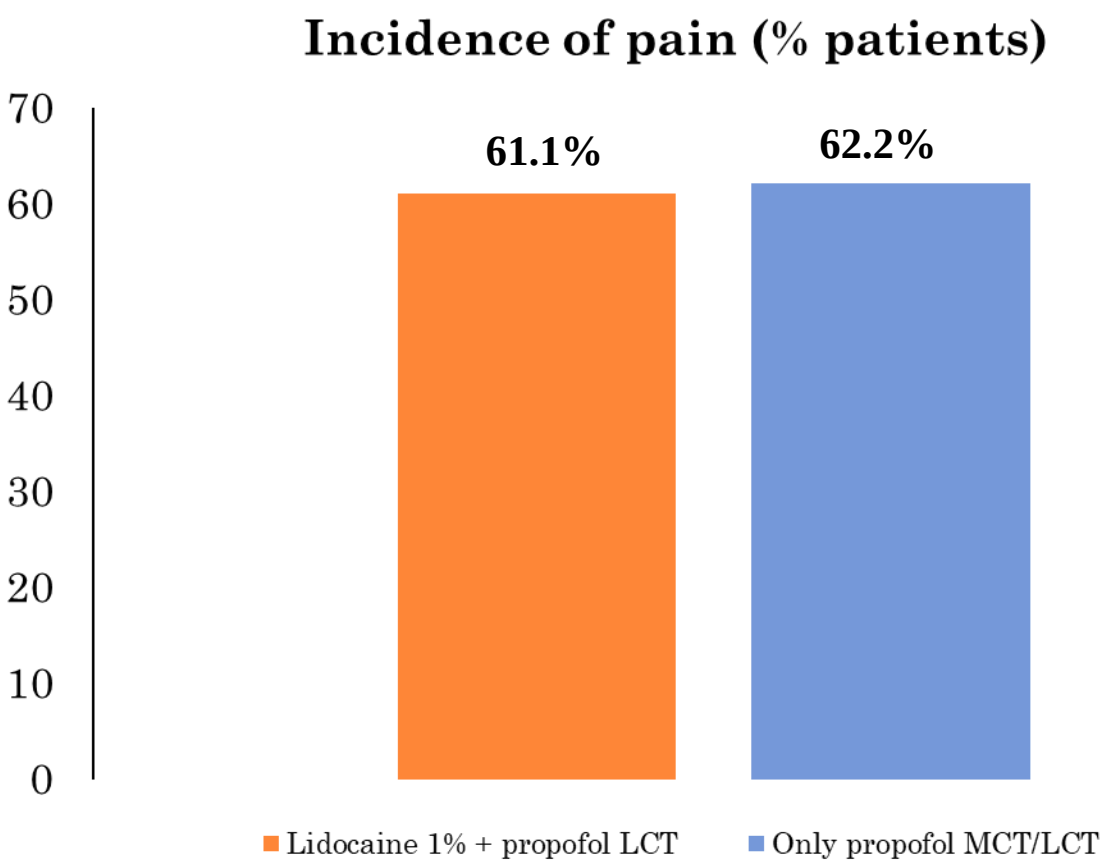
PROPOFOL-LCT VERSUS PROPOFOL-MCT/LCT WITH OR WITHOUT LIDOCAINE

- Double Blind RCT
- N=360
- Intervention & results

Intervention groups	Incidence of pain (%)
Group 1: pretreatment of lidocaine 1% and propofol LCT	61.1
Group 2: pretreatment of lidocaine 1% and propofol MCT/LCT	46.7
Group 3: pretreatment of saline and propofol MCT/LCT	62.2
Group 4: pretreatment of saline and propofol LCT mixed with lidocaine 1%	55.6

1. *Burimsittichai R, et al. J Med Assoc Thai 2006; 89 Suppl 3: S86-91.*

INCIDENCE OF PAIN ON INJECTION OF PROPOFOL MCT/LCT WAS NOT DIFFERENT FROM THAT CAUSED BY PROPOFOL LCT WITH PRETREATMENT OF LIDOCAINE



1. *Burimsittichai R, et al. J Med Assoc Thai 2006; 89 Suppl 3: S86-91.*

British Journal of Anaesthesia 95 (2): 222–5 (2005)
doi:10.1093/bja/aei156 Advance Access publication May 13, 2005

BJA

PAEDIATRIC ANAESTHESIA

Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation *versus* propofol with added lidocaine

Y. Nyman[1]*, K. von Hofsten[1], A. Georgiadi[2], S. Eksborg[2 3] and P. A. Lönnqvist[1]

- N=83 children (age range 2–18 yr)
- Intervention
  - group pL, n=42 (Propofol-Lipuro® (MCT-LCT))
  - group pD, n=41 Diprivan® (LCT) + lidocaine

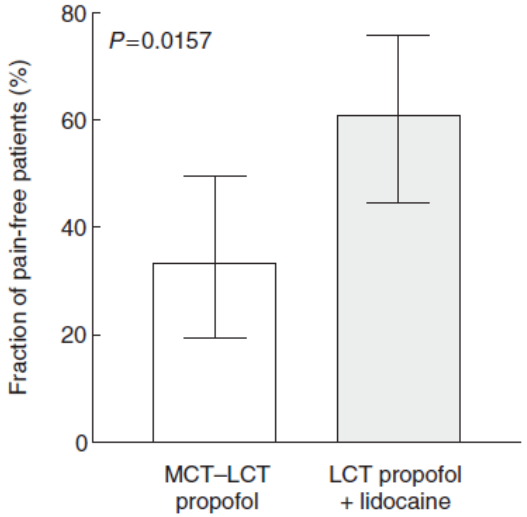


Fig 1 Children with pain-free injection of propofol (error bars indicate 95% confidence interval).

Significantly fewer patients had an entirely pain-free propofol injection in group pL (33.3%) than in group pD (61.0%) (P=0.016).

1. Nyman Y, et al. British Journal of Anaesthesia 2005; 95 (2): 222–5

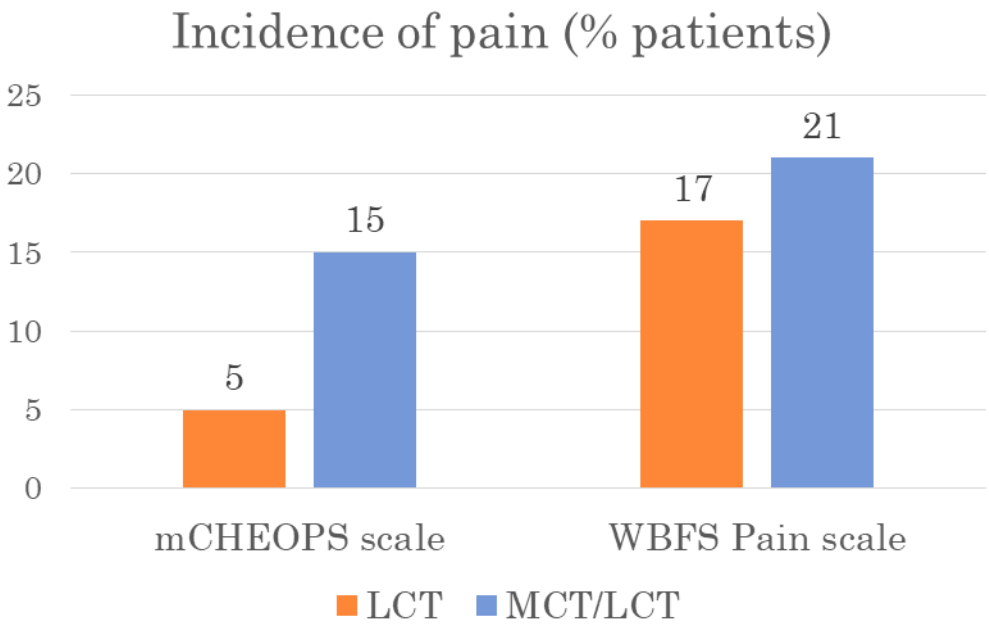
Original Article

Injection pain of propofol in children: A comparison of two formulations without added lidocaine

Serbülent Gökhan Beyaz, Ali Eman[1]

Department of Anaesthesiology, Sakarya University Medical School, Sakarya, [1]Ipekyolu State Hospital of Van, Republic of Turkey

- Interventions
  - Group LCT: Propofol LCT 1%
  - Group MCT/LCT received propofol



Propofol MCT/LCT does not decrease injection pain; contrary to the general assumption, it causes more pain than propofol LCT in children

1. *Gökhan Beyaz, et al. Journal of Anaesthesiology Clinical Pharmacology 2012; 28(3)*

PROPOFOL COMPOSITION

Sr No	Item	Qty/ml	Use
1.	Propofol IP	10 mg	Active drug
2	Soybean oil refined USP	100mg	Emulsifier
3	Egg Lecithin purified	12mg	Emulsifier
4	Disodium EDTA dihydrate	0.05mg	Antimicrobial & preservative
5	Glycerin IP	22.5mg	Antimicrobial & preservative
6	NaOH	QS	To adjust pH
7	Nitrogen gas	QS	To adjust pH
8	Water for injection	QS to 1mL	

SUMMARY

- **DCGI:** Both the formulations are DCGI approved
- Differences between the two propofol formulations were slight and not clinically significant.
- **Plasma concentrations** of propofol were not different between the two formulations
- **Induction time** was 14% longer with propofol with LCT/MCT compared to propofol with LCT only emulsion
- **Emergence time** (return of consciousness) was not significantly different in groups administered propofol LCT/MCT and propofol with LCT as bolus, however emergence time was marginally longer for LCT/MCT administered as infusion over 30 mins (P=0.04)
- **Octanoate**, a metabolite of medium-chain triglycerides, was elevated with propofol LCT/MCT, however elevated concentrations were below the toxic levels.

CONTD…..

- **Effect on pain:** Two most efficacious interventions to reduce pain on injection of propofol were use of the antecubital vein, or pretreatment using lidocaine in conjunction with venous occlusion when the hand vein was chosen.
- **Lidocaine** is always used with propofol (LCT/MCT or LCT only) to prevent pain at injection site
- **Pain** is always high in propofol administered without lidocaine
- Pain on injection has been linked to the **free propofol drug concentration**
- **Equivalent reduction in pain** with Propofol-LCT with pre-treatment of lidocaine or Propofol-MCT/LCT alone
- **Pretreatment with lidocaine** before Propofol-MCT/LCT is required for additional reduction of pain

CONTD…

- **In children:**

- Significantly fewer patients had an entirely pain-free propofol injection in LCT/MCT group (33.3%) than in LCT group (61.0%) (P=0.016).
- Propofol MCT/LCT does not decrease injection pain; contrary to the general assumption, it causes more pain than propofol LCT in children

CONCLUSION

Propofol LCT is considered an **essential agent** owing to its properties like:

- Pharmacokinetic characteristics along with its **sedative and amnestic properties**
- It can cross the blood brain barrier rapidly due to its **high lipophilic activity**, leading to an **onset of action within 30 to 60 seconds**.
- It has **short recovery profile** due to rapid metabolism, with **effects lasting for 4 to 8 minutes.**

Gut Liver 2021;15:562-568

Thank You

PROPOFOL LCT/MCT

Propofol LCT

Propofol is water insoluble, it has been formulated as a 1% solution in a fat emulsion containing 10% soybean oil consisting of long chain triglycerides (LCT).

Hence, it is known as Propofol LCT

Pain on injection with propofol

- Propofol is a membrane irritant
- Three out of five patients experience pain on injection of propofol, with one of these patient s reporting severe or excruciating pain[1]
- About 60% of patients experience pain on injection with standard propofol alone that is, wit hout any preventive measures

Pain on injection has been linked to the free propofol drug concentration[2]

1. *BMJ 2011; 342: d1110*
2. *Sim JY, et al. Br J Clin Pharmacol 2009; 67: 316-325*

INTERVENTIONS FOR REDUCING PAIN

- Propofol injection in antecubital vein (Injection into a larger vein)
- ***Lidocaine pretreatment with venous occlusion***
- Opioid pretreatment
- Ketamine pretreatment
- NSAID pretreatment

Propofol emulsion, medium and long chain triglycerides

Propofol LCT/MCT

What is LCT/MCT

A nutritional lipid emulsion consisting of both coconut oil-derived medium chain triglycerides (MCTs) and soybean oil-derived long chain triglycerides (LCTs).

Propofol composition: Differences between LCT only and MCT/LCT

Sr No	Propofol LCT	Propofol MCT/LCT	Use
1.	Propofol	Propofol	Active drug
2	Soybean oil, Egg Lecithin (LCTs)	Soya oil, Egg lecithin, oleic acid (LCTs)	Emulsifier
3	-	Medium chain triglycerides	Emulsifier
4	Disodium EDTA dihydrate	-	Antimicrobial & preserv ative
5	Glycerin	Glycerol	Antimicrobial & preserv ative
6	NaOH	NaOH	To adjust pH
7	Nitrogen gas	-	To adjust pH
8	Water for injection	Water for injections	

CLINICAL EFFICACY OF PROPOFOL LCT/ MCT vs. PROPOFOL LCT

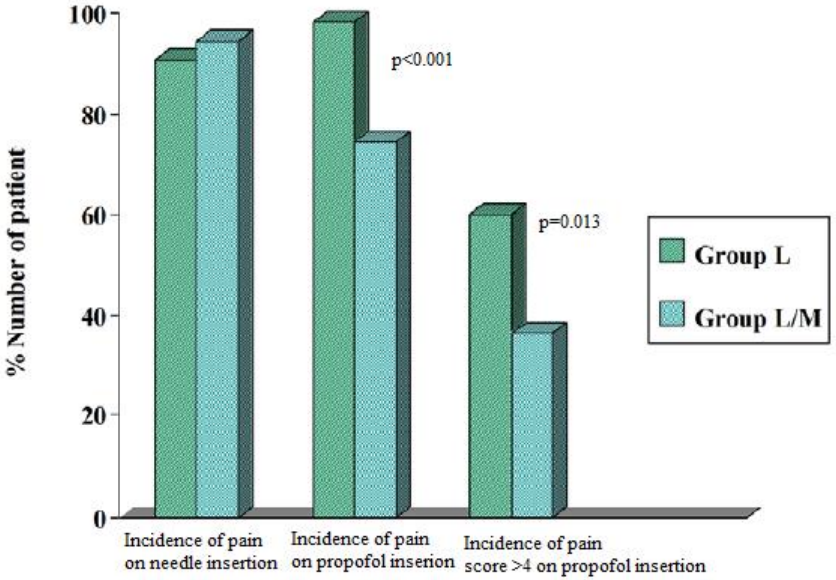
Anaesth Intensive Care 2005; **33:** 351-355

Comparative Study Between Propofol in a Long-chain Triglyceride and Propofol in a Medium/Long-chain Triglyceride During Sedation with Target-controlled Infusion

	Propofol LCT (n=20)	Propofol MCT/LCT (n=20)
Pain		
None	7 (35)	12 (60)
Mild	7 (35)	5 (25)
Moderate	3 (15)	3 (15)
Severe*	3 (15)	0 (0)
Incidence of pain†	13 (65)	8 (40)
Incidence of hypotension	5 (25)	6 (30)
Recovery time (min)	14.5±4.3	15.2±4.2

Propofol MCT/LCT was associated with significantly less incidence and less intensity of pain on injection than the standard preparation of propofol LCT

A Comparison of Propofol-LCT with Propofol-LCT/MCT on Pain of Injection



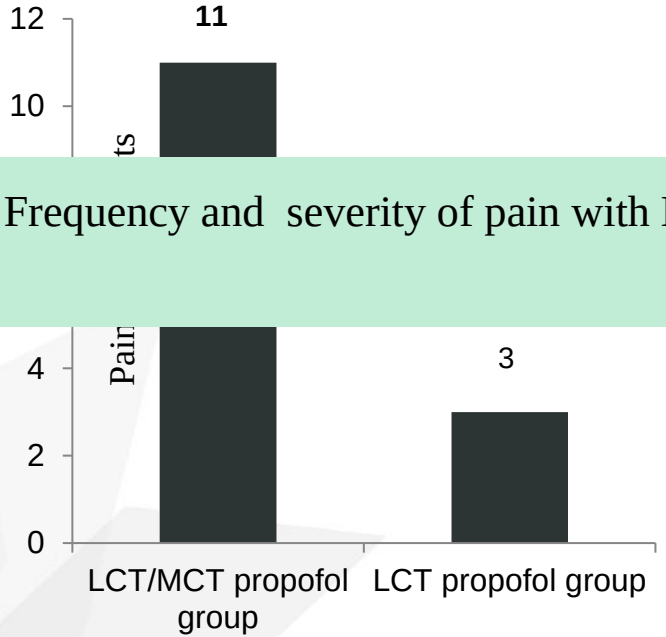
Significantly greater incidence of pain in group L vs. group L/M

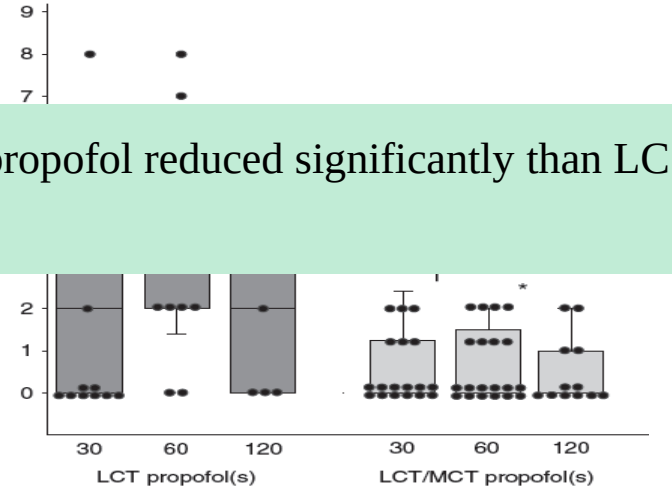
1% Propofol-LCT(Group L) [n=55];1% Propofol-LCT/MCT (Group L/M) [n=55]
n=female patients elective obstetric and gynecological procedures

J Med Assoc Thai 2007;90 (12); 2683-8

Significantly greater no. of pain free patients were observed with LCT/MCT propofol vs. LCT propofol

Significantly higher maximum pain score with LCT propofol (median 4) vs. LCT/MCT propofol (median 0.5)



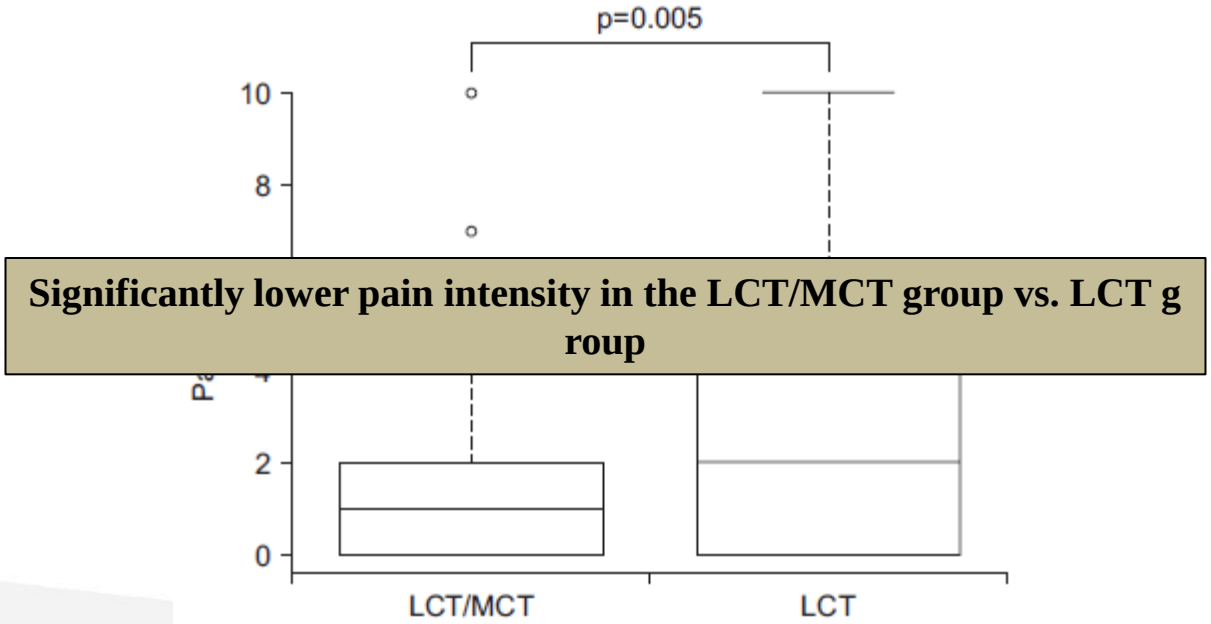


Frequency and severity of pain with LCT/MCT propofol reduced significantly than LCT propofol

n=patients scheduled for elective surgery ; LCT Propofol group (n=23); LCT/MCT Propofol group (n=22)

Acta Anaesthesiol Scand 2006; 50: 568—571

LCT/MCT propofol versus conventional LCT propofol

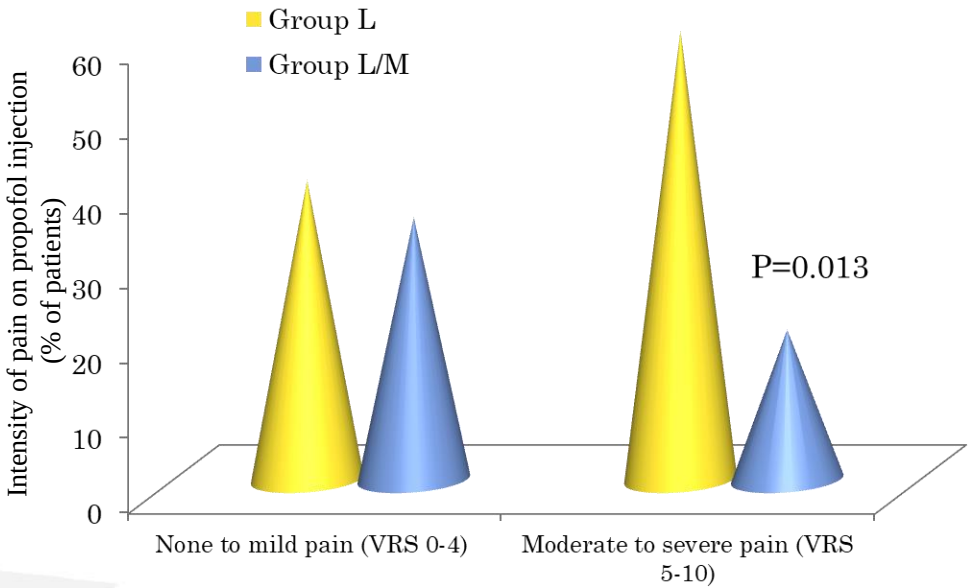


Significantly lower pain intensity in the LCT/MCT group vs. LCT g roup

LCT/MCT (n=68) and LCT (n=61); n= patients undergoing esophagogastroduodenoscopy (EG D)

Gut Liver 2021;15:562-568

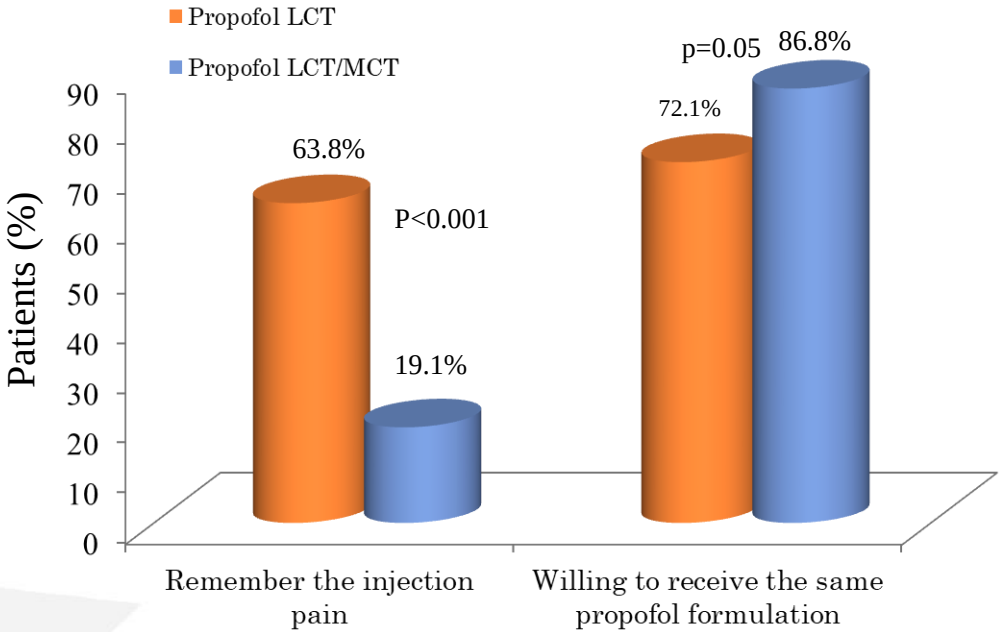
Significantly greater intensity of pain with group L vs. group L/M



Group L (n=55);Group L/M (n=55);
n=female patients elective obstetric and gynecological procedures
VRS=Verbal rating score 0-10 (with 0 = no pain,1-4 = mild; 5-7 = moderate, 8-10 = severe or the worst pain imaginable)

J Med Assoc Thai 2007;90 (12); 2683-8

Patient's that receive LCT/MCT propofol were less likely to remember the pain and more willing to use the same agent



LCT/MCT (n=68) and LCT (n=61); n= patients undergoing esophagogastroduodenoscopy (EGD)

Gut Liver 2021;15:562-568

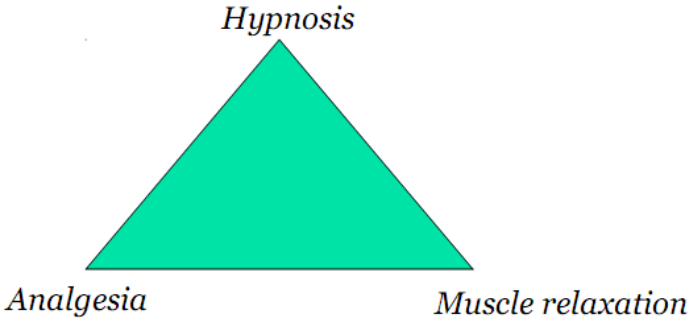
SUMMARY

- Propofol is an excellent IV induction agent with a speedy recovery.
- Pain on IV injection of Propofol LCT is its major setback.
- The most important factor for the pain on injection is the free concentration of propofol in the aqueous phase.
- Maintaining similar pharmacological properties as standard propofol, emulsions of MCT/LCT have smaller propofol concentrations in the aqueous phase.
- New formulation MCT/LCT propofol is found to reduce the incidence and intensity of pain on injection

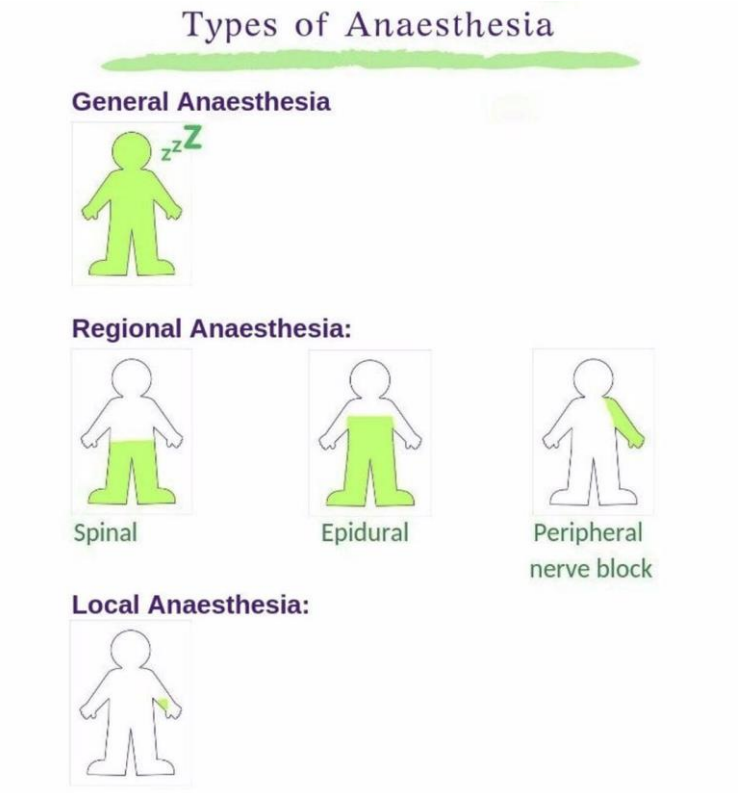
“ISOFLURANE” & “SEVOFLURANE”

INTRODUCTION TO ANASTHESIA

- **Anaesthesia** means Blocking of perception of **pain** and other **sensations**
- This allows patients to undergo **surgery** and other procedures without the suffering and pain they would otherwise experience



TYPES OF ANASTHESIA



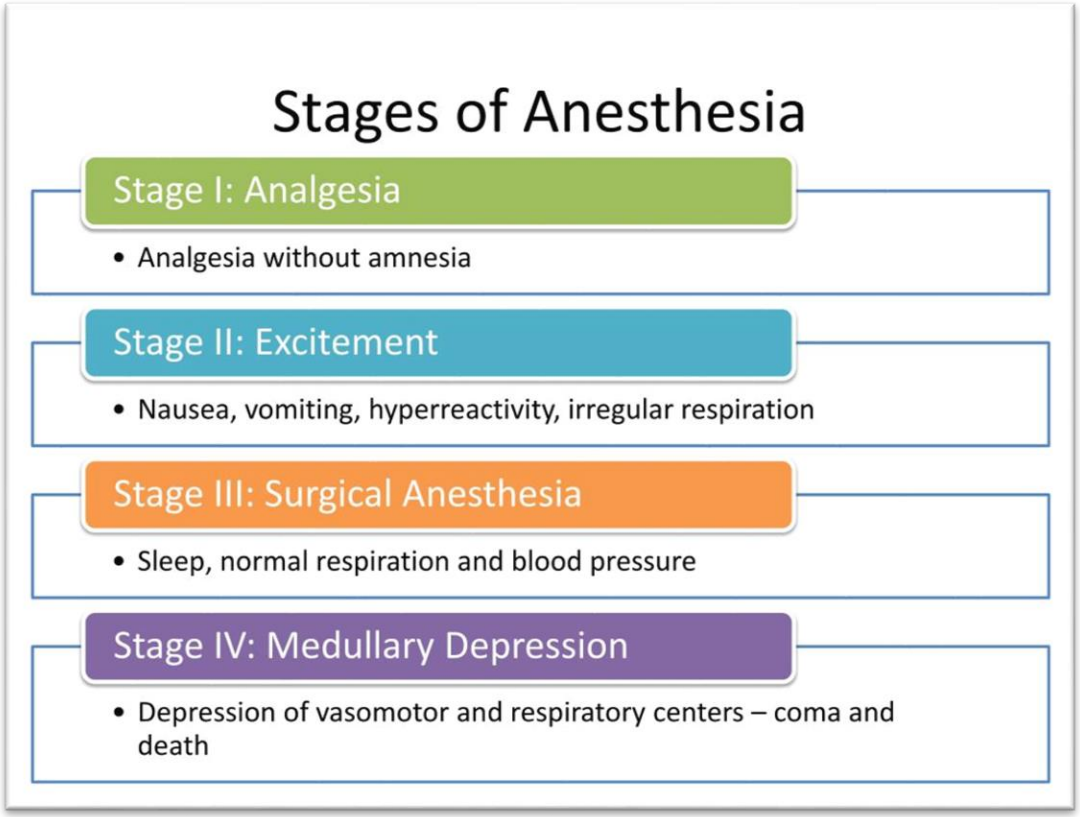
GENERAL ANESTHESIA

All the protective reflexes are suppressed.

Amnesia (Inability to recall) is the main characteristic, while analgesia and muscle relaxation may be present, to varying degrees..

The medications used in general anesthesia are given by **intravenously** or by **inhalation**.

STAGES OF GENERAL ANESTHESIA



I.V. ANESTHETICS

- Intravenous injection works faster than inhalation. This minimizes the excitatory phase (Stage 2) and thus may reduce complications

- Dexmedetomidine
- Midazolam
- Ketamine
- Thiopental
- Opioids eg., Fentanyl, Morphine
- Propofol

INHALATIONAL GENERAL ANESTHETICS

- Inhalation anesthetics are used for induction and maintenance of general anesthesia in the operating room

- Halothane
- Enflurane
- **Isoflurane**
- **Sevoflurane**
- Nitrous oxide
- Desflurane

NCBI bookshelf

NEED FOR INHALATIONAL ANESTHESIA?

IV agents – Induction occurs more quickly & smoothly

The **lack of a means for continuously measuring the depth of anesthesia** is perhaps the most important reason for **avoiding the use of i.v. anesthetics for anesthesia maintenance**

In contrast, use of **inhaled anesthetics for maintenance** of anesthesia provides greater control of the depth of anesthesia **because sophisticated devices are available for monitoring the concentration of the inhaled anesthetic agent delivered to the patient**

Am J Health-Syst Pharm—Vol 61 Oct 15, 2004 Suppl 4

HISTORY OF INHALATIONAL ANAESTHESIA

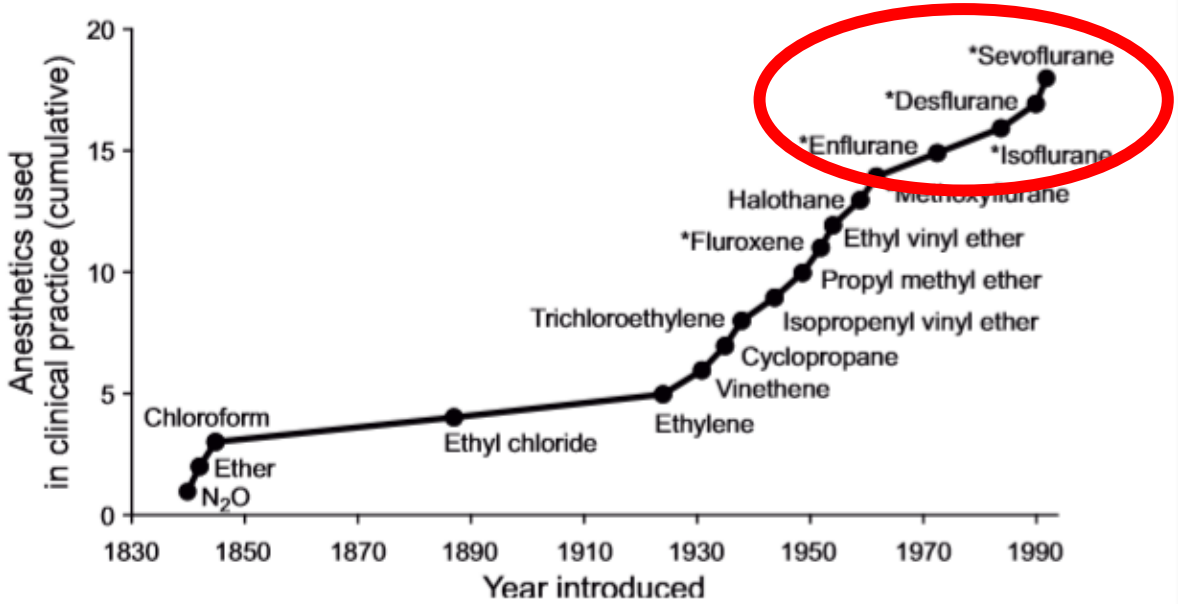


Fig. 1. History of inhalation anesthetics. *Compounds containing fluorine. Adapted from ref. 196 with permission from McMahon Publishing Group.

The first reports of the use of inhalation anaesthetics began to emerge in the 1840s.

Safety issues were quickly recognized and the search for better inhalation agents began

Since then halothane and enflurane have passed through common usage

The inhalation agents used in modern practice include isoflurane, sevoflurane, and desflurane and N_2O

CNSDrugReviews,Vol.7,No.1,2001

Mechanism of action of Inhalational anaesthetics

Sub-classification	Site	Mode of action
Macroscopic	Brain & spinal cord	Decrease transmission of noxious afferent information & spinal efferent neuronal activity reducing movement response to pain. Mediates hypnosis and amnesia
Microscopic	Synapses and axons	Inhibit excitatory presynaptic channel activity mediated by neurotransmitters Serotonin & Glutamine Augments inhibitory activity mediated by $GABA_A$
Molecular	pre- and post-synaptic membranes	GABA binding to its receptor leads to opening of a chloride channel leading to increased Cl^- ion conductance and hyperpolarization of the cell membrane, thereby increasing the depolarization threshold

ALDRETE'S SCORING SYSTEM

- Commonly used scale for determining when people can be safely discharged from the post-anesthesia care unit (PACU) to either the postsurgical ward or to the second stage (Phase II) recovery area
- A score 9 was required for shifting from OT to post-surgical ward

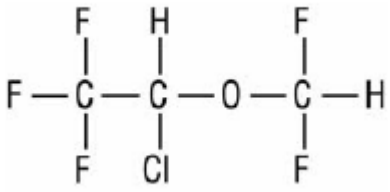
Activity	Respiration	Circulation	Consciousness	Oxygen Saturation
2: Moves all extremities voluntarily/ on command	2:Breaths deeply and coughs freely.	2: BP + 20 mm of preanesthetic level	2:Fully awake	2: Spo2 > 92% on room air
1: Moves 2 extremities	1: Dyspneic, shallow or limited breathing	1: BP + 20-50 mm of preanesthetic level	1: Arousable on calling	1:Supplemental O2 required to maintain Spo2 >90%
0: Unable to move extremities	0: Apneic	0: BP + 50 mm of preanestheic level	0: Not responding	0: Spo2 <92% with O2 supplementation

J Clin Anesth 1995;7:89 – 91;

ISOFLURANE

INTRODUCTION

- A non-flammable liquid administered by vaporizing, is a general inhalation anaesthetic drug



INDICATION

ADULTS: Induction and Maintenance of general anaesthesia

PEDIATRICS: Maintenance of general anaesthesia

PHARMACOKINETICS

- Isoflurane undergoes minimal biotransformation in man
- In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

DOSAGE

- **PRE-MEDICATION:**

❑ Premedication should be selected according to the need of the individual patient

❑ The use of anticholinergic drugs is a matter of choice.

DOSAGE

In order to be able to accurately control the precise concentration of isoflurane, vaporisers that have been specially calibrated for isoflurane should be used.

- **Induction of anaesthesia:**

a starting concentration of 0.5% is recommended

Concentrations of 1.3-3.0% usually bring about surgical anaesthesia within 7 to 10 minutes.

- **Maintenance of anaesthesia:**

a concentration of 1.0-2.5% with the simultaneous administration of N_2O and O_2.

- **Recovery:**

A concentration must be reduced to 0.5% at the end of the operation, or to 0% during closure of the wound to allow prompt recovery.

CONTRAINDICATIONS

- Known sensitivity
- Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS & PRECAUTION

- Perioperative Hyperkalemia (↑potassium)
- Malignant Hyperthermia

SPECIAL POPULATION

- **PREGNANCY**:

Category C: no adequate and well-controlled studies in pregnant women

- **NURSING MOTHERS**:

not known whether this drug is excreted in human milk.

DRUG INTERACTION

- Isoflurane potentiates the muscle relaxant effect of all muscle relaxants

COMMON ADVERSE EFFECTS

- Respiratory depression
- hypotension
- Arrhythmias
- Shivering
- Nausea
- Vomiting

Post-operative period

US PI

CLINICAL EVIDENCES

Isoflurane: An Anesthetic for the Eighties?

John G. Wade, MD,* and Wendell C. Stevens, MD†

- Relatively low solubility in blood in relation to anaesthetic dose (halothane & Enflurane)
- Lack of arrhythmogenic effect
- Provision of good muscle relaxation
- Absence of central nervous system excitation

ANESTHESIA AND ANALGESIA V~I 60, NO 9. September 1981

CONCLUSION

We believe isoflurane is a significant improvement over earlier potent inhalational anesthetics.

ANESTHESIA AND ANALGESIA V~I 60, NO 9. September 1981

Anesthesiology
55:559–576, 1981

REVIEWS

BRYAN E. MARSHALL, M.D., Editor

Isoflurane: A Review

Edmond I. Eger II, M.D.*

- Physically stable
- Low blood solubility
- Absence of myocardial depression
- Potentiates the effects of muscle relaxant
- Absence to produce seizure activity

CONCLUSION

- Isoflurane is likely to play a major role in the future delivery of anaesthetic care.

Anesthesiology 55:559-576, 1981

Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety *

E. M. Spencer and S. M. Willatts

Intensive Care Unit, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK

AIM: : To compare isoflurane with midazolam for prolonged sedation in ventilated patients.

N= 60 (17 to 80 yrs)

RESULTS:

Patients were maintained at the ideal level of sedation for 70.07% of time in the isoflurane group and for 67.4% of time in the midazolam group.

Intensive Care Med (1992) 18:415-421

RECOVERY RESULTS

	ISOFLURANE	MIDAZOLAM
RESPOND TO COMMAND (MIN)	10	90
WRITE ADDRESS (h)	1	21
SPONTANEOUS VENTILATION (h)	0.25	3
EXTUBATION (h)	0.9	15
RETURN TO WARD (h)	48.5	50

Intensive Care Med (1992) 18:415-421

CONCLUSION

Isoflurane is a useful agent for prolonged sedation of ventilated patients and does not have any adverse effect on the cardiorespiratory system or on hepatic, renal or adrenal function

Intensive Care Med (1992) 18:415-421

LIMITATION OF ISOFLURANE

SOLUBILITY[1]

High solubility (1.4)-

slower onset of action*

IRRITANT TO AIRWAY [1]

Slower RECOVERY [2]

PEDIATRICS[2]

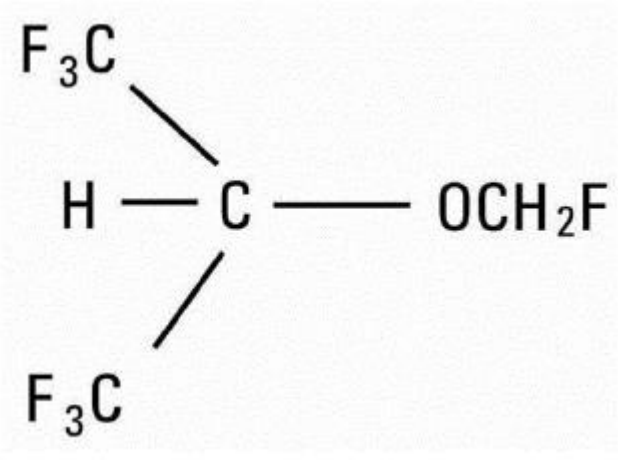
*General Anesthesia- Steven I. Ganzberg, Daniel A. Haas, in Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017

[1] Can J Anesth/J Can Anesth (2016) 63:1128–1139
[2] Indian J Anaesth. 2011 Jul-Aug; 55(4): 364–369.

SEVOFLURANE

INTRODUCTION

Sevoflurane, volatile liquid for inhalation, a nonflammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anesthetic drug.



INDICATION

- Induction and maintenance of general anaesthesia **in adult and paediatric patients of all ages**, including full term neonates

DOSAGE

PRE-MEDICATION

- No specific premedication is either indicated or contraindicated with sevoflurane.
- The decision as to whether or not to premedicate and the choice of premedication is left to the discretion of the anesthesiologist

US PI

DOSAGE

Anaesthesia Induction:

Induction with sevoflurane may be achieved by inhalation of 0.5-1.0% sevoflurane in oxygen (O_2) with or without nitrous oxide (N_2O), increasing by increments of 0.5-1.0% sevoflurane, to a maximum of 8% in adults and children until the required depth of anaesthesia is achieved.

Maintenance of Anaesthesia:

maintained by inhalation of 0.5-3% sevoflurane in O_2 with or without concomitant use of N_2O.

US PI

CONTRAINDICATION

- Hypersensitivity
- Malignant hyperthermia
- Confirmed hepatitis
- Hepatic dysfunction

WARNING/PRECAUTION

- Respiration should be continuously monitored
- Malignant Hyperthermia
- Perioperative Hyperkalaemia
- Renal Impairment
- Neurosurgery & Neuromuscular Impairment
- Seizures

DRUG INTERACTION

- Alpha and Beta-sympathomimetic agents
- Succinylcholine
- Amphetamine derivatives
- Non-selective MAO inhibitors
- Epinephrine/Adrenaline
- Beta blockers
- Barbiturates
- Neuromuscular Blocking Agents

SPECIAL POPULATION

- **Pregnancy:** No adequate and well-controlled studies
- **Labour and Delivery*:*** Caution should be exercised in obstetric anaesthesia due to the relaxant effect of sevoflurane on the uterus and increase in uterine haemorrhage
- **Breastfeeding*:*** Caution should be exercised

COMMON ADVERSE REACTIONS

- **In adult patients**: hypotension, nausea and vomiting
- **In elderly patients:** bradycardia, hypotension and nausea
- **In paediatric patients:** agitation, cough, vomiting and nausea

UK PI

CLINICAL EVIDENCES

Sevoflurane Versus Isoflurane: Induction and Recovery Characteristics with Single-Breath Inhaled Inductions of Anesthesia

Mark H. Sloan, MD, Pattilyn F. Conard, MA, CRNA, Peter K. Karsunky, MD, and Jeffrey B. Gross, MD

Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, Connecticut

- **AIM**: To compare the efficacy of sevoflurane with that of isoflurane for single breath inhaled induction in adult outpatient
- N= 50 (18 to 76 yrs)
- **Premedication**: Midazolam 0.01-0.03 mg/kg IV
- Either 5 % sevoflurane 0r 5 % isoflurane in 50% N2O:O2 mixture
- Anasthesia maintained with 70% N2O in O2 and either sevoflurane or isoflurane

Anesth Analg 1996;528-32

RESULTS

	Sevoflurane	Isoflurane
Time to loss eye reflex (induction time):	75 +/- 3 s	67 +/- 4 s
Time required to open the eyes	8.1 min	10.6 min
Respond to command	8.0 min	9.9 min
Orientation to surrounding	9.9 min	12.6 min
Legible for discharge from recovery room	56 min	65 min
Legible for discharge from hospital	120 min	133 min

Anesth Analg 1996;528-32

RESULTS

Table 1. Complications During Induction of Anesthesia

	Sevoflurane	Isoflurane
Overall		
Complicated	14 (56%)*	23 (92%)
Uncomplicated	11 (44%)	2 (8%)
Event[a]		
Coughing	4 (16%)†	19 (76%)
Laryngospasm	7 (28%)	5 (20%)
Breath holding	4 (16%)	7 (28%)
Airway obstruction	6 (24%)	11 (44%)
Excessive secretions	0	0
Excitement	3 (12%)	6 (24%)
Shivering	1 (4%)	0

* $P < 0.005$ versus isoflurane.
† $P < 0.001$ versus isoflurane.
[a] Each "complicated" patient experienced one or more "events."

Table 2. Complications During Emergence

	Sevoflurane	Isoflurane
Overall		
Complicated	15 (60%)	14 (56%)
Uncomplicated	10 (40%)	11 (44%)
Event[a]		
Coughing	12 (48%)	9 (36%)
Laryngospasm	1 (4%)	0
Breath holding	0	1 (4%)
Excessive secretions	2 (8%)	1 (4%)
Excitement	1 (4%)	1 (4%)
Shivering	4 (16%)	6 (24%)

There are no significant differences between anesthetics.
[a] Each "complicated" patient experienced one or more "events."

Anesth Analg 1996;528-32

CONCLUSION

Sevoflurane is more suitable than isoflurane for single breath induction, because it produces a smoother induction with lower incidence of complications and better patient acceptance

Anesth Analg 1996;528-32

A Phase III, Multicenter, Open-Label, Randomized, Comparative Study Evaluating the Effect of Sevoflurane *versus* Isoflurane on the Maintenance of Anesthesia in Adult ASA Class I, II, and III Inpatients

- **AIM**: to compare the clinical efficacy and safety of sevoflurane and isoflurane when used for maintenance of anaesthesia in adults undergoing surgical procedures
- N= 555

Journal of Clinical Anesthesia 8:557-563, 1996

RESULTS

Table 3. Anesthetic Exposure and Subsequent Recovery Times

	Sevoflurane	Isoflurane
Emergence† (min)	11.0	16.4
Response to commands‡ (min)	12.8	18.4
Orientation§ (min)	17.2	24.7
Eligibility for discharge from PACU	139.2	165.9

Journal of Clinical Anesthesia 8:557-563, 1996

RESULTS

Table 6. Comparison of the Most Commonly Reported Adverse Events

Adverse Event	Sevoflurane (n = 272), n (%)	Isoflurane (n = 283), n (%)
Nausea	75 (28%)	84 (30%)
Somnolence	59 (22%)	61 (22%)
Vomiting	44 (16%)	46 (16%)
Chills	34 (13%)	42 (15%)
Dizziness	26 (10%)	38 (13%)
Increased cough	26 (10%)	41 (15%)

Note: There were no statistically significant differences between groups.

Table 4. Clinical Success Rates

	Sevoflurane	Isoflurane
Patients having no untoward effect		
during induction period*	249/272 (92%)	257/283 (91%)
during maintenance	242/272 (89%)	250/283 (88%)
on emergence†	148/270 (55%)	136/281 (39%)
overall	129/270 (48%)‡	110/281 (39%)

Journal of Clinical Anesthesia 8:557-563, 1996

CONCLUSION

Sevoflurane anesthesia, as compared with isoflurane, may be advantageous in providing a smoother clinical course with a more rapid recovery.

Journal of Clinical Anesthesia 8:557-563, 1996

Awakening Properties of Isoflurane, Sevoflurane, and in Pediatric Patients After Craniotomy for Supratentorial Tumours

Ayman A. Ghoneim, MD, Magda S. Azer, MD,**
Hossam Z. Ghobrial, MD, and Mohammed A. El Beltagy, MD†*

- **AIM**: to compare the inhalational anesthetics isoflurane & sevoflurane in pediatric patients undergoing craniotomy for excision of supratentorial tumors
- N= 60 (7 to 18 yrs) (20 pts each grp: Isoflurane & sevoflurane)
- **Premedication**: midazolam 0.1mg/kg IV
- Maintenance of anesthesia was obtained using intravenous infusion of fentanyl at rate of 0.5mg/kg/h, atracurium at rate of 0.5mg/kg/h together with administration of the inhalational anesthesia (either isoflurane/sevoflurane) according to the study group

J Neurosurg Anesthesiol 2015;27:1–6

RESULTS

TABLE 2. Intraoperative Characteristics

Parameters	Isoflurane Group (n = 20)	Sevoflurane Group (n = 20)
Surgery time (min)	178.6	169
Anesthesia time (min)	227.6	208.8
Total amount of fentanyl	150	152
MAC-hour anesthetic agent	3.45	3.12
Patients required medication for bradycardia (atropine)	0	2 (10)
Patients required medication for tachycardia (labetalol)	0	0
Patients required medication for hypotension (ephedrine)	0	0
Patients required medication for hypertension (increased depth of anaesthesia)	2 (10)	0
Patients required medication for increased brain swelling (mannitol and furosemide)	2	3
Temperature at extubation (°C)	36.2	36.2

Data are represented as mean ± SD or n (%).

J Neurosurg Anesthesiol 2015;27:1–6

RESULTS

TABLE 3. Emergence, Extubation Time, and Interval Elapsed to Reach Aldrete Score ≥ 9

Parameters	Isoflurane Group (n = 20)	Sevoflurane Group (n = 20)
Extubation time (min)	21.25	14.
Emergence time (min)	15.53	11.
Interval to reach Aldrete score ≥ 9 (min)	35.6	29.2
No. patients with extubation time < 15 min	0	11 (55)

Data are represented as mean ± SE of mean or n (%).
*$P < 0.001$ in comparison with isoflurane group.

Side effects

	ISOFLURANE	SEVOFLURANE
Postoperative vomiting	3 (15%)	2 (10%)
Post operative shivering	3 (15%)	4 (20%)
Neurological complications	None	None

J Neurosurg Anesthesiol 2015;27:1–6

CONCLUSION

Sevoflurane can be used to facilitate early emergence from anaesthesia in neurosurgical paediatric patients as it is suitable for emergence

J Neurosurg Anesthesiol 2015;27:1–6

A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics

J Anesth (2017) 31:764–778

Jorge D. Brioni[1] · Shane Varughese[1] · Raza Ahmed[1] · Berthold Bein[2]

Table 2 Emergence and discharge times following anesthetic discontinuation (adult patients)

Study	Anesthetic agents compared	Extubation/LMA removal (min ± SD)	*P* value	Eye opening (min ± SD)	*P* value	Discharge (min ± SD)
Campbell et al. [17]	SEVO ($n = 271$)	17.8 ± 2.9	NS	11.0 ± 0.6	<0.001	139.2 ± 15.6[a]
	ISO ($n = 281$)	12.8 ± 3.1		16.4 ± 0.6		165.9 ± 16.3[a]

Table 5 Emergence and discharge times following anesthetic discontinuation (elderly patients)

Peduto et al. [41]	SEVO ($n = 50$)	8 (2–35)[a]	<0.01	8.5 (2–57)[a]	<0.01	21 (5–69)[a]
	ISO ($n = 54$)	11 (2–35)[a]		12.5 (3–47)[a]		27.5 (9–180)[a]

Table 4 Emergence and discharge times following anesthetic discontinuation (pediatric patients)

Jindal et al. [9]	SEVO ($n = 42$)	5.3 ± 2	<0.001	4.4 ± 2.7	<0.001	
	ISO ($n = 42$)	9.7 ± 4.2		8.1 ± 3.1		
Singh et al. [31]	SEVO ($n = 40$)	6.4 ± 3.3	<0.001	7.8 ± 3.4	<0.001	140.7 ± 49.3[a]
	ISO ($n = 40$)	10.7 ± 4.6		12.8 ± 5.6		146 ± 43.3[a]

A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics

J Anesth (2017) 31:764–778

Jorge D. Brioni[1] · Shane Varughese[1] · Raza Ahmed[1] · Berthold Bein[2]

In conclusion, over the past 20 years, sevoflurane has been used in nearly 900 million patients and has demonstrated a positive benefit–risk ratio over a broad spectrum of patients.

J Anesth (2017) 31:764–778

Comparison of Recovery Profile After Ambulatory Anesthesia with Isoflurane, Sevoflurane A Systematic Review

- **AIM**: focused on postoperative recovery and complications using different anesthetic techniques.
- Database searched since 1966 to 2002

Table 4. Characteristics and Conclusions of Studies Included in the Meta-Analysis

Study	Comparison between	Number of patients	Type of surgery	Was N_2O used?	Early recovery	Intermediate recovery	Authors conclusions
Smith (47)	Isoflurane vs Sevoflurane	62	Elective surgery	Yes	NR	No differences	No differences
Sloan (48)	Isoflurane vs Sevoflurane	50	Amb Surg procedures	Yes	No differences	No differences	Sevoflurane better recovery profile
O'Hara (49)	Isoflurane vs Sevoflurane	47	Gynecological surgery	Yes	Favours sevoflurane	No differences	Sevoflurane better
Eriksson (50)	Isoflurane vs Sevoflurane	49	Gynecological Laparoscopy	Yes	No differences†	No differences	Early recovery better in sevoflurane
Philip (51)	Isoflurane vs Sevoflurane	246	Amb Surg procedures	Yes	Favours sevoflurane	No differences	Sevoflurane better
Elcock (52)	Isoflurane vs Sevoflurane	180	Arthroscopy	Yes	NR	NR	No differences

Anesth Analg 2004;98:632–41

ADIS DRUG EVALUATION

Paediatr Drugs 1999 Apr-Jun; 1 (2): 127-153
1174-5878/99/0004-0127/$13.50/0

Sevoflurane in Paediatric Anaesthesia

A Review

Karen L. Goa, Stuart Noble and *Caroline M. Spencer*

Adis International Limited, Auckland, New Zealand

- **Sevoflurane is a preferred anaesthetic agent for induction and maintenance of paediatric anaesthesia** because of its rapid induction and recovery characteristics, lack of pungency and agreeable odour, and acceptable cardiovascular profile.

British Journal of Anaesthesia **85 (2)**: 305–7 (2000)

Which is most pungent: isoflurane, sevoflurane

M. F. TerRiet*, G. J. A. DeSouza, J. S. Jacobs, D. Young, M. C. Lewis, C. Herrington and M. I. Gold

- The irritability gradient was: Isoflurane > sevoflurane
- Sevoflurane is least irritating agent for inhalation

British Journal of Anaesthesia 85 (2): 305-7 (2000)

Isoflurane Vs Sevoflurane

LESSER SOLUBILITY (0.68)
(Rapid induction)

LESSER IRRITANT
TO AIRWAYS

FASTER RECOVERY

APPROVED FOR
INDUCTION &
MAINTENANCE OF
PEDIATRIC ANESTHESIA

THANK YOU

Lidfast Jelly

Lignocaine HCL Jelly 2% w/v, 30 gm (sterile)

Also available

LIDFAST

Lignocaine Inj.2%, 30 ml

Introduction

- LIDFAST (Lignocaine/Lidocaine) is a medication use to numb tissues in a specific area. Lignocaine may also be applied directly to the skin for numbing

Numb: Loss of sensation

Mechanism of action

Lidocaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses.

Pharmacokinetics

Pharmacokinetic data

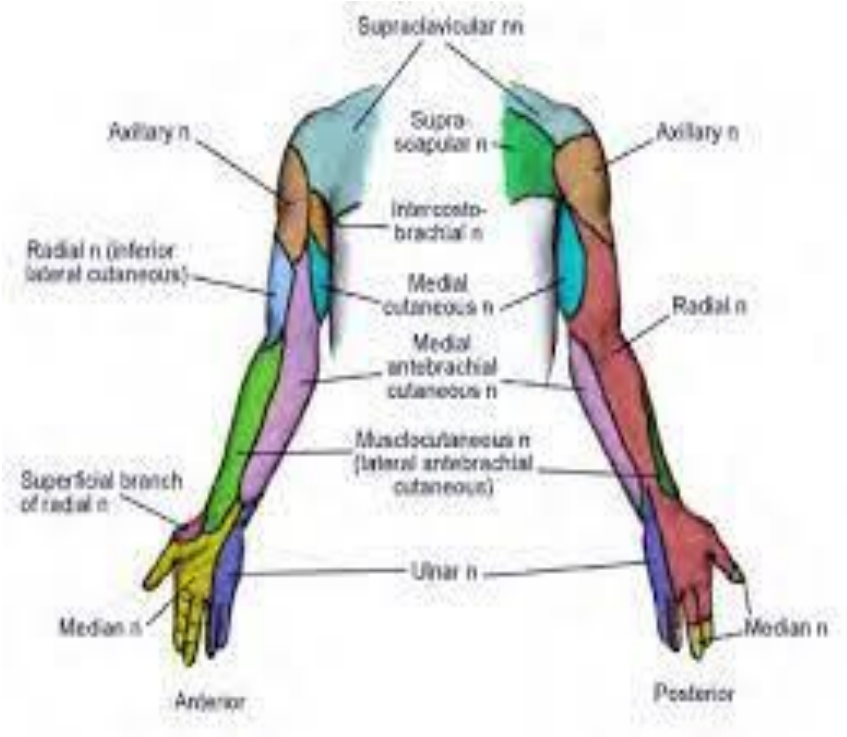
Bioavailability	35% (oral) 3% (topical)
Metabolism	Liver, 90% CYP3A4-mediated
Onset of action	within 1.5 min
Biological half-life	1.5–2 h
Duration of action	10 to 20 min(IV), 0.5 to 3 h (injection)
Excretion	Kidney

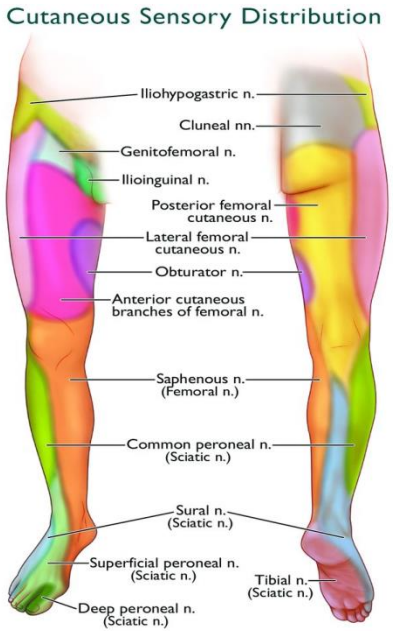
Indication

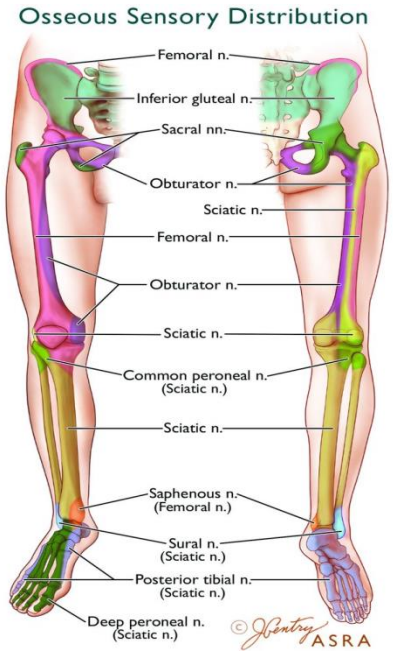
- For Topical anaesthesia & Lubrication – Jelly

- For Local anaesthesia & nerve block (regional anaesthesia) – Injection

    - Local – Percutaneous injection
    - Peripheral nerve block techniques such as brachial plexus/ Femoral block
    - Epidural


Supraclavicular nn
Axillary n
Supra-scapular n
Axillary n
Intercosto-brachial n
Radial n (inferior lateral cutaneous)
Medial cutaneous n
Radial n
Medial antebrachial cutaneous n
Musculocutaneous n (lateral antebrachial cutaneous)
Superficial branch of radial n
Ulnar n
Median n
Median n
Anterior
Posterior


Cutaneous Sensory Distribution
Iliohypogastric n.
Cluneal nn.
Genitofemoral n.
Ilioinguinal n.
Posterior femoral cutaneous n.
Lateral femoral cutaneous n.
Obturator n.
Anterior cutaneous branches of femoral n.
Saphenous n. (Femoral n.)
Common peroneal n. (Sciatic n.)
Sural n. (Sciatic n.)
Superficial peroneal n. (Sciatic n.)
Deep peroneal n. (Sciatic n.)
Tibial n. (Sciatic n.)


Osseous Sensory Distribution
Femoral n.
Inferior gluteal n.
Sacral nn.
Obturator n.
Sciatic n.
Femoral n.
Obturator n.
Sciatic n.
Common peroneal n. (Sciatic n.)
Sciatic n.
Saphenous n. (Femoral n.)
Sural n. (Sciatic n.)
Posterior tibial n. (Sciatic n.)
Deep peroneal n. (Sciatic n.)
ASRA

Target Customers

- Anaesthesiologist
- Intensivist
- Gynecologist

Dosage - Jelly

- Anaesthetic Lubrication for Intubation

  Apply moderate amount to the external surface of endotracheal tube shortly before use. Not to exceed 600 mg/ 12 hrs.

- Urethral Surface Anaesthesia

  Female: Instil 2-5ml jelly (60-100mg) into urethra

  Male : Instil 15 ml (300mg lignocaine) into urethra

  Total dose of 30 ml (600mg) is usually required

Dosage - Injection

Duration of action: 1.5 to 2 hours when given epidurally, and up to 5 hours when given as a peripheral nerve block.

Adults: Dose should be individualized. Maximum individual dose should not exceed 4.5 mg/kg. Maximum total dose does < 300 mg.

For intravenous regional anesthesia; the dose administered should < 4mg/kg in adults.

Children: The dose should not exceed 3mg/kg

For local anesthesia & lubrication

Rx

LiDFAST

Lignocaine HCl Jelly 2% w/v, 30gm (Sterile)

Prompt & Sterile Anaesthesia

- An anaesthetic lubricant during endotracheal intubation[1]
- Relieves post operative sore throat[2]
- Safe & effective in ocular anesthesia[3]

Also Available

Endotoxin Free
Water for Injection

Bupibloc

Inj. Bupivacaine 0.5 % (100mg/ 20ml)

Bupibloc Heavy

Inj. Bupivacaine 0.5 % (20mg/ 4ml) & Dextrose Monohydrate 80mg/4ml

Introduction

- Bupibloc (Bupivacaine) is an anesthetic agent

- **Bupivacaine** is used as a Local & Regional (Epidural) anesthesia.

Mechanism of action

Bupivacaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses.

Pharmacokinetics

Bioavailability	n/a
Protein binding	95%
Metabolism	Liver
Onset of action	Within 15 min
Biological half-life	3.5 hours (adults) 8.1 hours (neonates)
Duration of action	2 to 8 hr.
Excretion	Kidney, 4–10%

Indication

Local or Regional anaesthesia or analgesia for surgery

- For oral surgery procedures
- For obstetrical procedures

Regional anaesthesia

Nerve block

Epidural

NOT RECOMMENDED FOR INTRAVENOUS

Target Customers

- Anaesthesiologist

Dosage

	Dose (mg)	Onset (min)	Duration (hrs)
Epidural	75-150	15-30	2-3
Nerve block	50-175	15-30	4-8

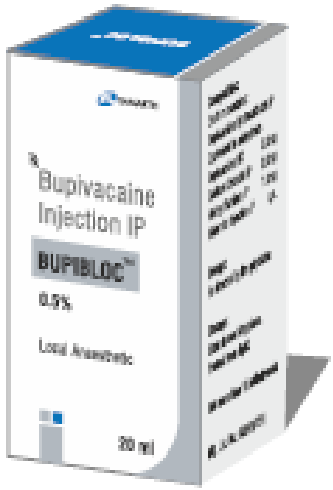
In peripheral nerve block, obstetrical anesthesia & post-operative pain

℞ BUPIBLOC

Inj. Bupivacaine HCl (0.5%) 100mg/20ml

"THE LONG-ACTING SENSORY ANAESTHESIA"

- 29% more potent than levobupivacaine[1]
- No tissue damage, irritation & methemoglobinemia[2]



Ropifast

Ropivacaine Inj. 2mg/ml, 7.5mg/ml

Introduction

- ROPIFAST (Ropivacaine) is a long-acting, anaesthetic with both anaesthetic and analgesic effects.

- Ropivacaine has less Neurotoxicity and Cardiotoxicity

Mechanism of action

Ropivacaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses.

Pharmacokinetics

Bioavailability	87%–98% (epidural)
Metabolism	Hepatic (CYP1A2-mediated)
Biological half-life	1.6–6 hours (varies with administration route)
Excretion	Renal 86%
Onset of Action	10-20 mins
Duration of action	2-8 hrs

Indication

Ropivacaine is indicated for the production of local or regional anesthesia for surgery and for acute pain management.

Surgical Anesthesia: epidural block for surgery including cesarean section; major nerve block

Acute Pain Management: epidural ropivacaine is given in postoperative period or during labor (delivery of baby)

Target Customers

- Anaesthesiologist
- Intensivist

Dosage

Majorly given by Epidural

	Dose (mg)	Onset (min)	Duration (hrs)
Caesarean section	25-75	10-20	--
Nerve Block	175-250	15-30	5-8
Labor pain	20-40	10-15	0.5-1.5
Postoperative pain	12-28 mg/h	--	--

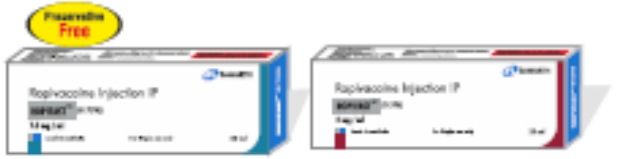
For surgical anesthesia, pain management
& obstetrical procedures

Rx ROPIFAST™

Inj. Ropivacaine 2mg/ml, 7.5mg/ml

The Cardio & Neuro Friendly
Local Anaesthetic

- Early mobilization & early recovery of patients[1]
- More favourable hemodynamic profile than levobupivacaine[1]
- Relief of postoperative & labour pain with less incidence of motor block[2]



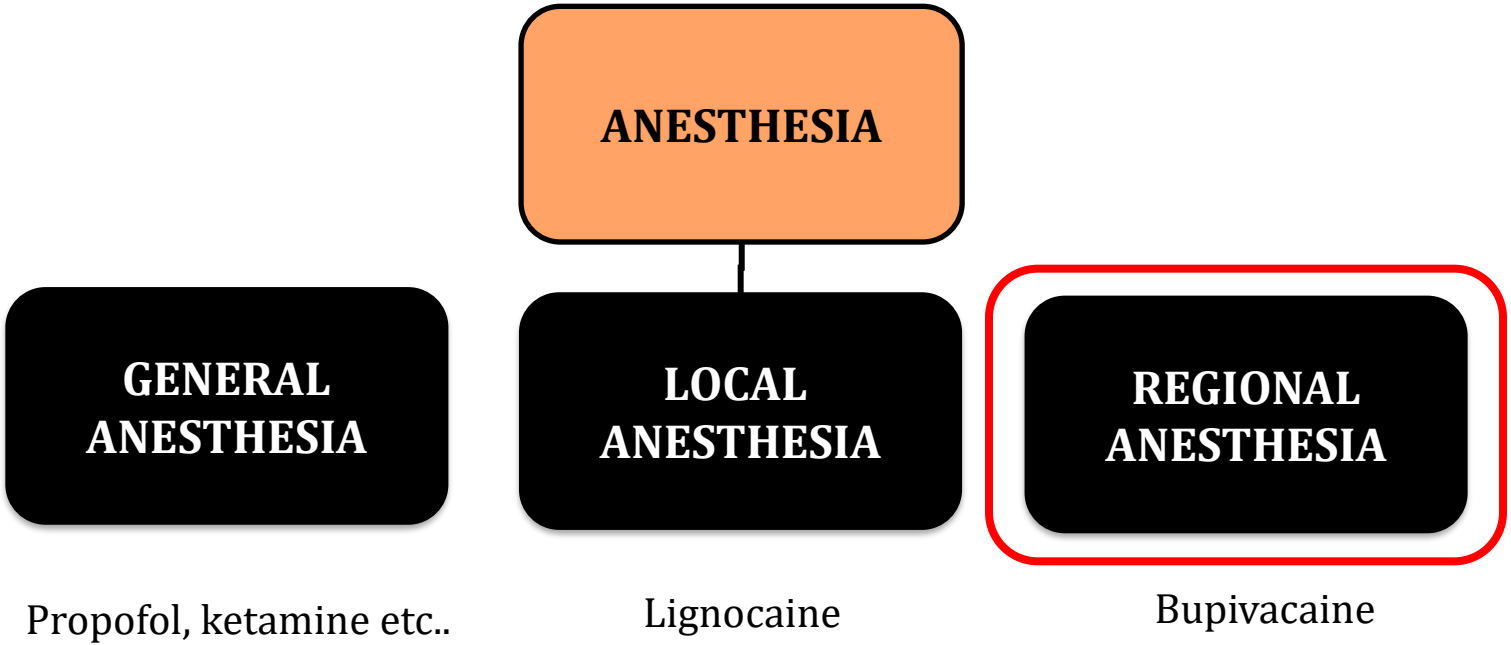
1. Int J Reprod Contracept Obstet Gynecol. 2017 Apr;6(4):1573-1577

Anaesthesia

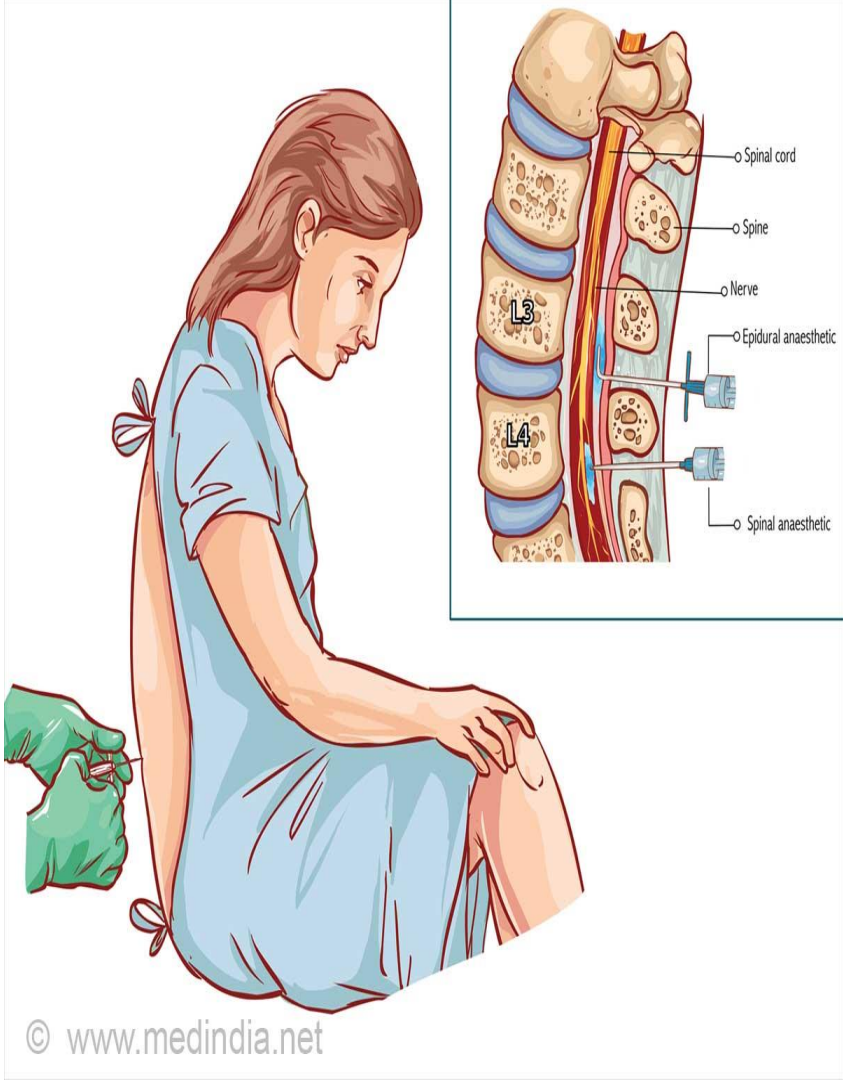
Anaesthesia means blocking of perception of **pain** and other **sensations**

This allows patients to undergo **surgery** and other procedures without the suffering and pain they would otherwise experience

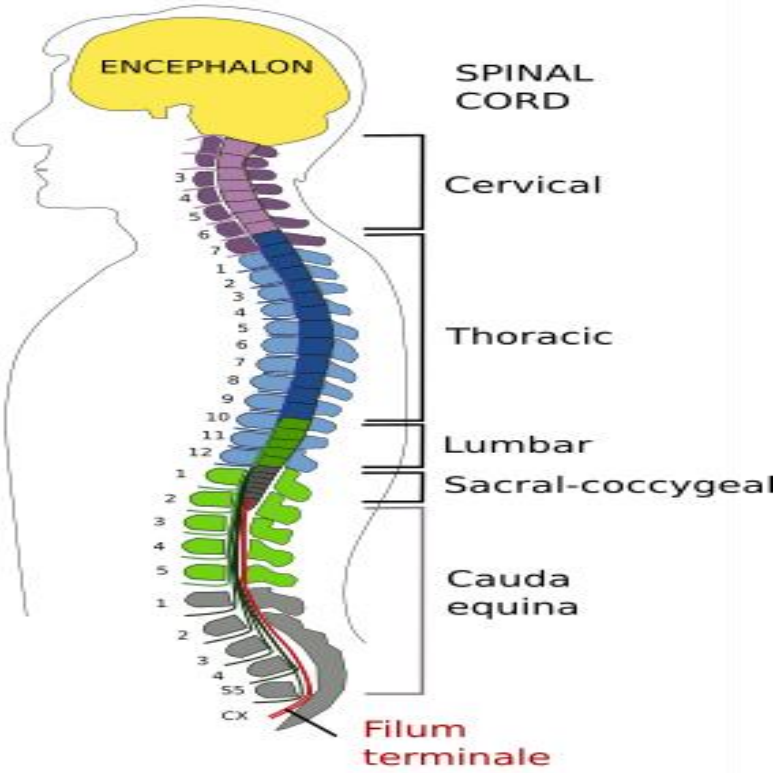
Types


ANESTHESIA
GENERAL ANESTHESIA
LOCAL ANESTHESIA
REGIONAL ANESTHESIA
Propofol, ketamine etc..
Lignocaine
Bupivacaine

Spinal/Epidural Anaesthesia



Vertebral column

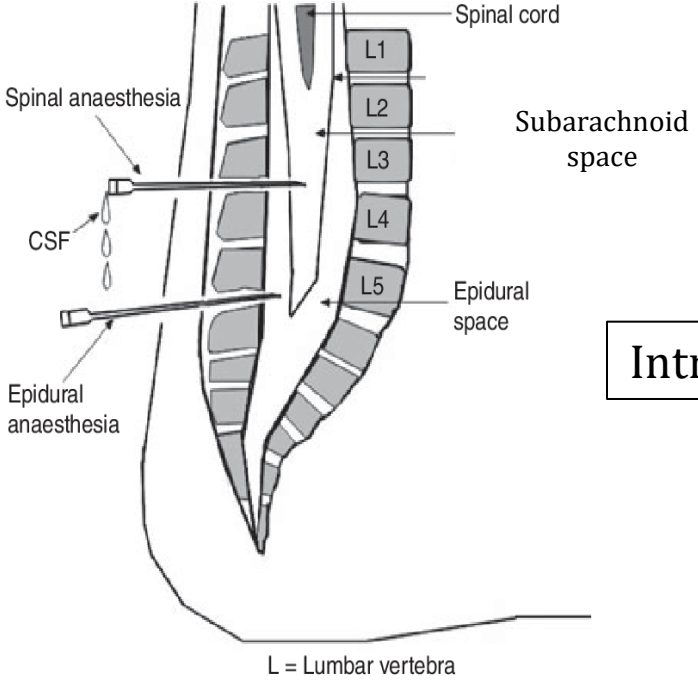


Spine consists of 33 vertebrae

Vertebrae	Number
Cervical	7
Thoracic	12
Lumbar	5
Sacral	5
Coccygeal	4

Injection Sites

Epidural space



Subarachnoid space

Epidural anaesthesia

Intrathecal/Spinal anaesthesia

Injection Sites

- Spinal anesthesia is often used for genital, urinary tract or lower body procedures.
- Epidural anesthesia is often used for surgery in the pelvis and legs.

Intrathecal/Spinal Drug Spread

Spinal anesthesia has the definitive advantage-

Profound nerve block can be produced by a simple injection with small amount of local anesthetic.

Greatest challenge of the technique-

- To **control the spread** of that local anesthetic through the cerebrospinal fluid (CSF)
- To **provide block that is adequate** (in both extent and degree) for the proposed surgery but without producing unnecessarily extensive spread and so increasing the risk of complications.

Br J Anaesth 2004; 93: 568-78

Factors Affecting Intrathecal Spread Of Local Anesthetics

Characteristics of the injected solution
- Baricity
- Volume/dose/concentration
- Temperature of injectate
- Viscosity
- Additives

Clinical technique
- Patient position
- Level of injection
- Needle type/alignment
- Intrathecal catheters
- Fluid currents
- Epidural injection

Patient characteristics
- Age
- Height
- Weight
- Sex
- Intra-abdominal pressure
- Spinal anatomy
- Lumbosacral cerebrospinal fluid volume
- Pregnancy

Br J Anaesth 2004; 93: 568-78

Lets understand Baricity in detail……

Understanding Baricity

Baricity, i.e. specific gravity, plays an important role in determining the extent to which local anesthetic agents spread within the cerebrospinal fluid (CSF) during subarachnoid block, and thus influences the extent of spinal anesthesia.[1]

The baricity is calculated as, ratio between the density of the anesthetic solution and the density of CSF. [2]

- If this ratio is 0.9990 (approaching 1), the solution is isobaric
- If the ratio is > than 1.0010, the solution is hyperbaric;
- if < than 0.9990, it is hypobaric.

Baricity of CSF is 1.0001-1.0006

1. Br J Anaesth 2004; 93: 568-78; 2. Br J Anaesth 2004; 92: 547±51

Difference between Isobaric/Plain and Hyperbaric

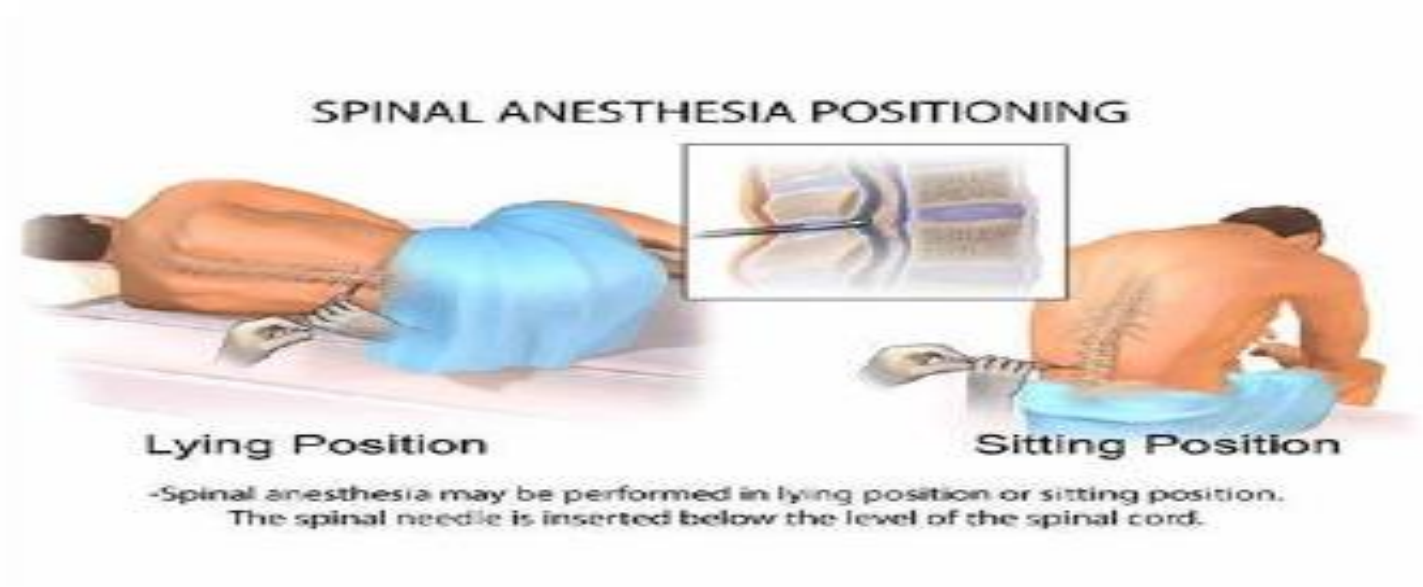
Isobaric/Plain	Hyperbaric
• Stays where you put it	• Settles to dependent aspect to the subarachnoid space- heavier than CSF
• LA has the same density or specific gravity as CSF (approaching 1)	• LA has a density or specific gravity that is greater than CSF (>1.0010)
• Produced by addition of NaCl	• Produced by addition of Dextrose
• Less predictable*	• More predictable*
• exhibit greater variability in effect and are less predictable, so that the block may either be too low, and therefore inadequate for surgery, or excessively high, causing side-effects.*	• greater spread in the direction of gravity and less interpatient variability.*

LA= Local anaesthetics

British Journal of Anaesthesia 92 (4): 547-51 (2004)

**British Journal of Anaesthesia 93 (4): 568–78 (2004)*

Patient Position



Drugs used in spinal anesthesia

- Lidocaine (5%): Onset of action occurs in 3 to 5 minutes with a duration of anesthesia that lasts for 1 to 1.5 hours
- Bupivacaine (0.75%): One of the most widely used local anesthetics; onset of action is within 5 to 8 minutes, with a duration of anesthesia that lasts from 90 to 150 minutes
- Tetracaine 0.5%
- Mepivacaine 2%
- Ropivacaine 0.75%
- Levobupivacaine 0.5%
- Chloroprocaine 3%

Abdulquadri M. Olawin; Spinal Anesthesia; StatPearls; Last Update: June 27, 2022.

Bupibloc

Plain

Inj. Bupivacaine 0.5 % (100mg/ 20ml)

BUPIBLOC (Bupivacaine) is an anesthetic agent

Bupivacaine is used as a Local & Regional (Epidural) anesthesia.

Composition:
Each ml contains:
Bupivacaine Hydrochloride IP
Equivalent to anhydrous
Bupivacaine HCl 5.0mg
Sodium Chloride IP 8.0mg

Limitations of Plain Bupivacaine

Exhibit greater variability in effect and are less predictable, so that the block may either be too low, and therefore inadequate for surgery, or excessively high, causing side-effects.

British Journal of Anaesthesia 93 (4): 568–78 (2004)

To Overcome the drawback of Bupivacine…..

INTRODUCING

Bupivacaine Hydrochloride in Dextrose Injection USP

BUPIBLOC Heavy™ **20 mg/4 ml**

Hyperbaric solution for spinal Anaesthesia, Preservative Free

Each ml contains:

Bupivacaine Hydrochloride IP equivalent to anhydrous Bupivacaine Hydrochloride	5 mg
Dextrose Anhydrous IP	80 mg

Hyperbaric Solution

- Hyperbaric solution must have a baricity of at least 1.0010or more than 1.0010*.

- The easiest and most widely used way to achieve hyperbaric solution is by the addition of dextrose to the anesthetic solution.

Dextrose is neurologically benign.

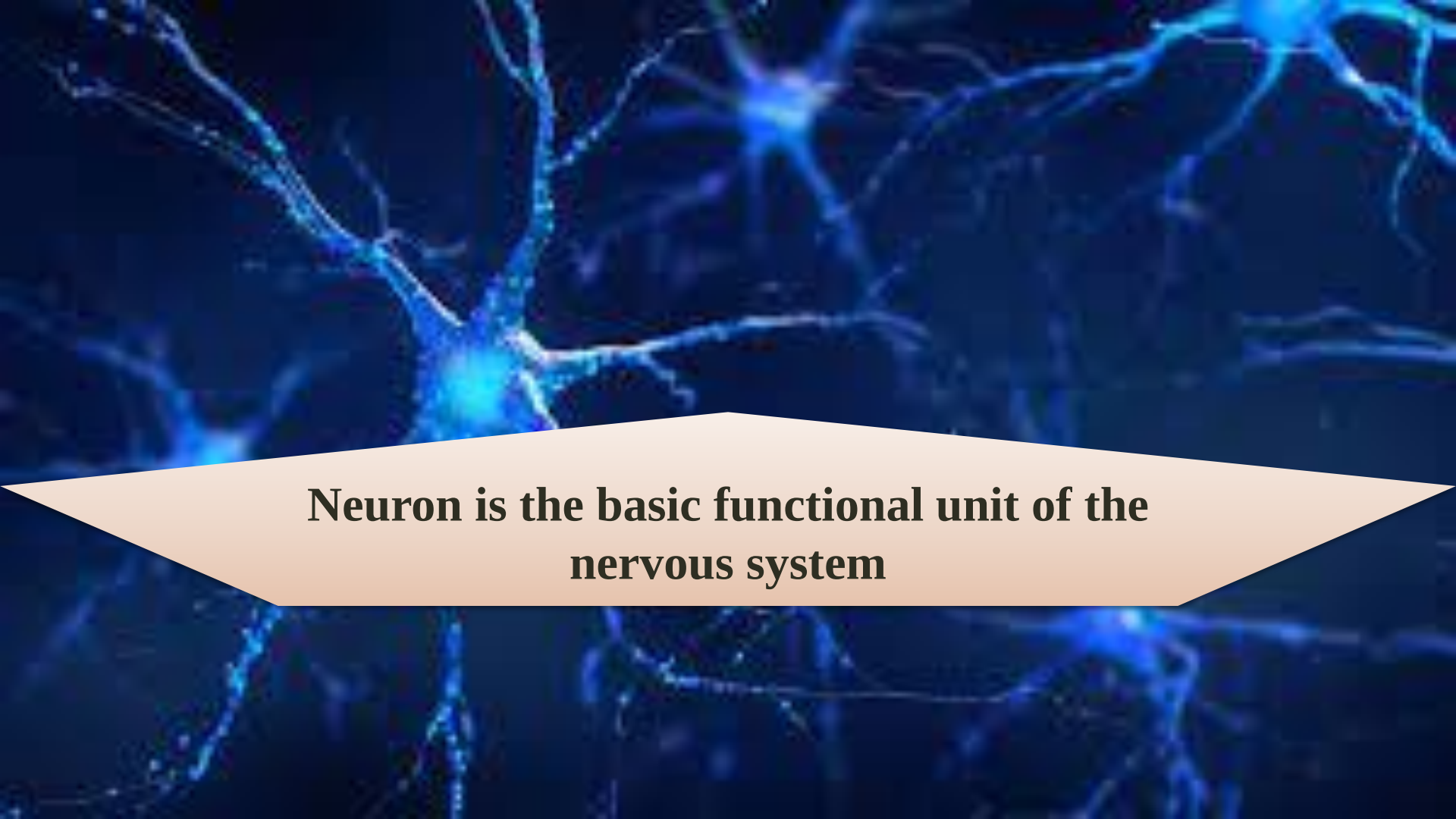
**British Journal of Anaesthesia 93 (4): 568–78 (2004)*
Anesth Analc. 1985;64:715-30.

Advantages of Dextrose Addition to Local Anesthetics

- Addition of dextrose to local anesthetics **increases the density of injectate**.
- **Provides a predictable and consistently high sensory block.**
- Dextrose concentrations between 8 and 30 mg/ml have shown **reliable and consistent spread for surgery.**
- **Addition of dextrose 80 mg/ml provides a predictable spread but to high thoracic levels.**

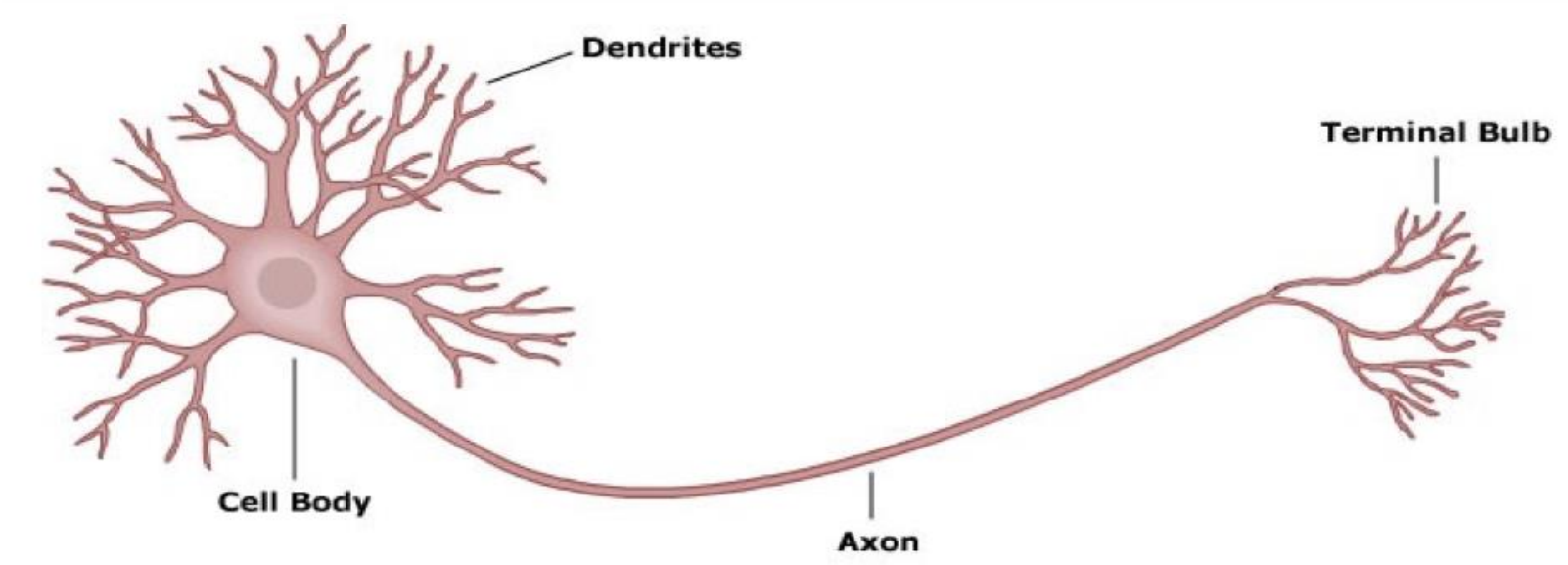
British Journal of Anaesthesia. 2004 Apr 1;92(4):547-51.

Mechanism of Action



Neuron is the basic functional unit of the nervous system

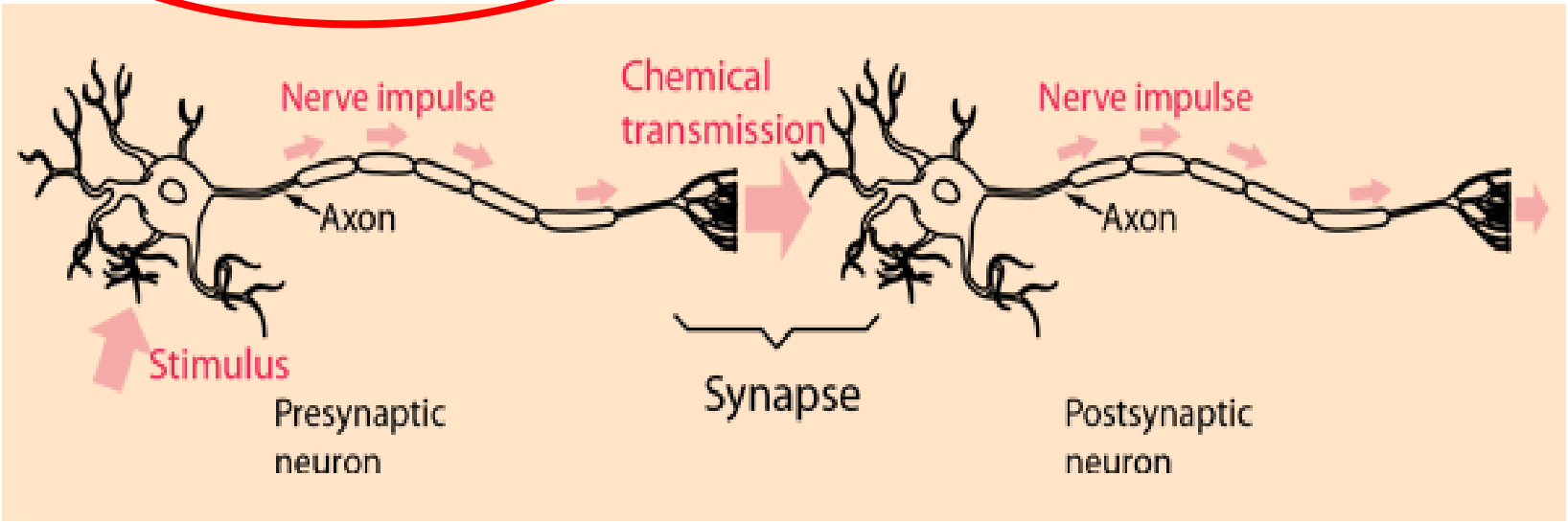
Structure of neuron



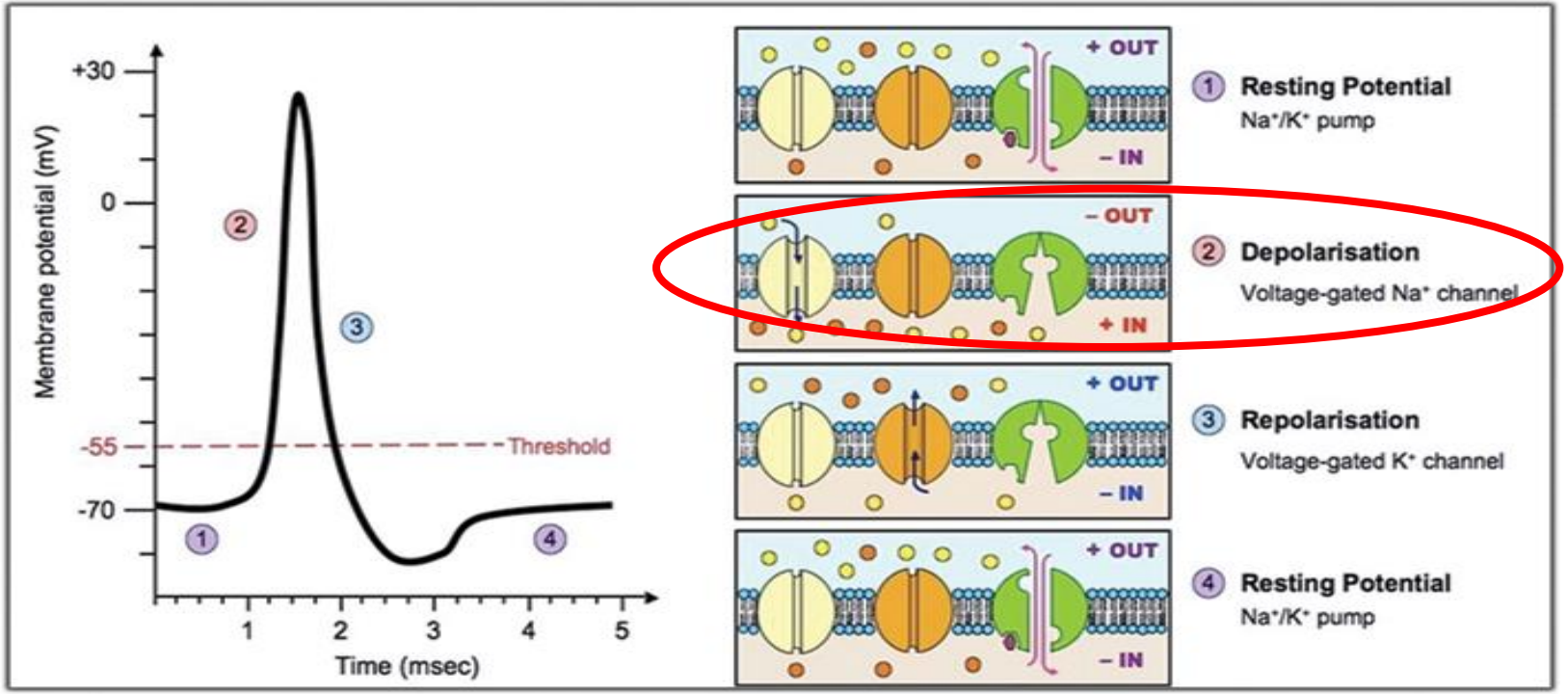
TRANSMISSION OF IMPULSES

Electrical
(within the neuron)

Chemical
(across the synapse)



Action Potential



Bupivacaine Mechanism of Action

Bupivacaine

↓

Block voltage-gated Na+ channels

↓

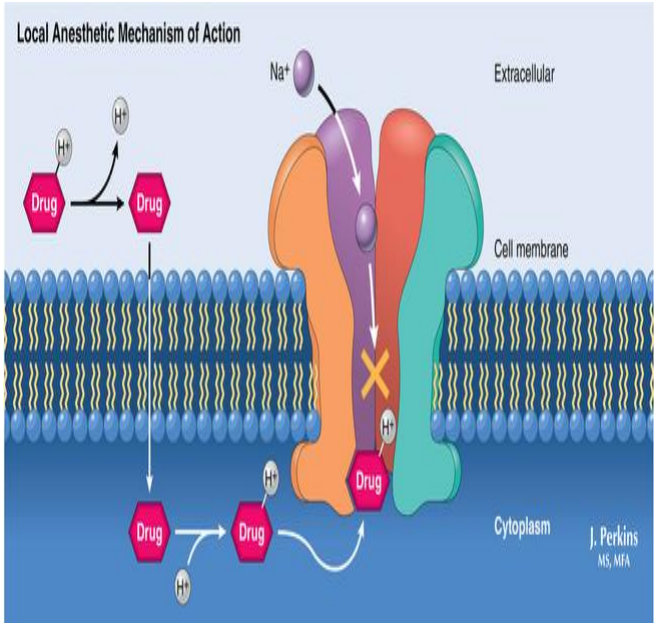
No entry of Na+ ions into

↓

No generation of action potential

↓

No generation and conduction of impluse to CNS



International PI UK, 2019

Bupibloc Heavy: Composition

Each ml contains:	
Bupivacaine Hydrochloride IP equivalent to anhydrous Bupivacaine Hydrochloride	5 mg
Dextrose Anhydrous IP	80 mg

Reference: Bupibloc PI. 2022

Bupibloc Heavy: Indication

Bupivacaine Heavy is indicated in adults and children of **all ages for intrathecal (subarachnoid) spinal anesthesia for surgery** (urological and lower limb surgery lasting 2–3 hours, abdominal surgery lasting 45–60 minutes).

Reference: CDSCO . as accessed on 7th Feb 2022- https://cdscoonline.gov.in/CDSCO/Drugs

Bupibloc Heavy: Dosage & Administration

Adults and children above 12 years of age

Indication	Dose	Time to onset of action	Duration
Intervention in the lower extremities, including hip surgery	2 – 4 ml (10 – 20 mg)	5-8 min	1.5 – 3 hours
Lower abdominal surgery (including caesarean section)	2 – 4 ml (10 – 20 mg)	5-8 min	1.5 – 3 hours
Urology surgery	1.5 – 3.0 ml (7.5 – 15 mg)	5-8 min	2 – 3 hours

There is no experience with administration of doses higher than 4 ml/20 mg of Bupivacaine Heavy

Bupibloc Heavy: Dosage & Administration

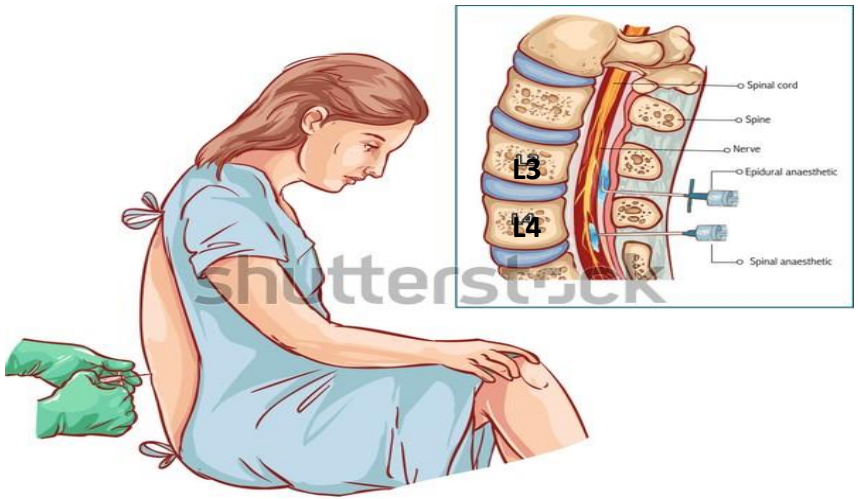
Paediatric population

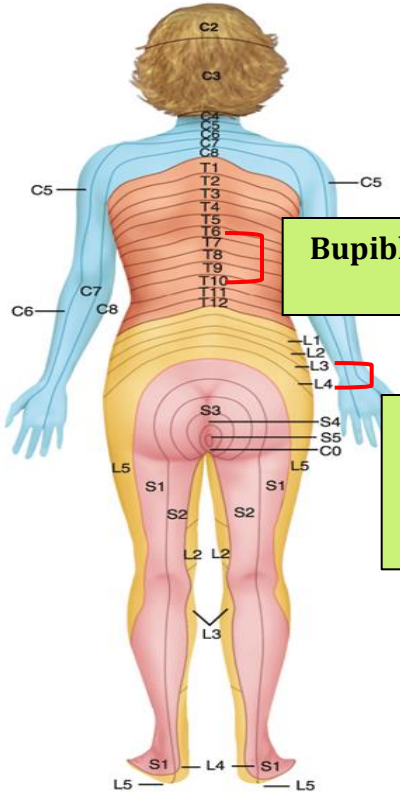
Dosage recommendations in neonates, infants and children up to 40 kg

Body weight (kg)	Dose (mg/kg)
<5 kg	0.40-0.50 mg/kg
5-15 kg	0.30-0.40 mg/kg
15-40 kg	0.25-0.30 mg/kg

Bupibloc Heavy: Method of Administration

For Intrathecal Use Only





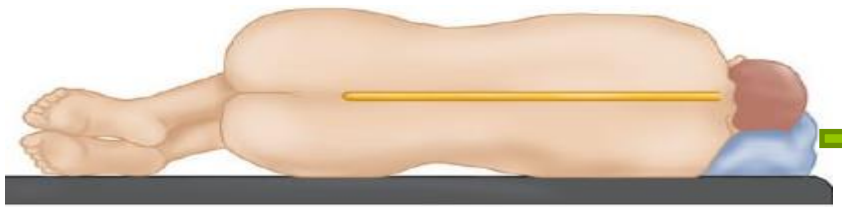
Bupibloc Heavy spreads to the T7–T10 spinal segments

When injected at the L3–L4 intervertebral space, with the patient in the sitting position, 3 ml of Bupivacaine Heavy

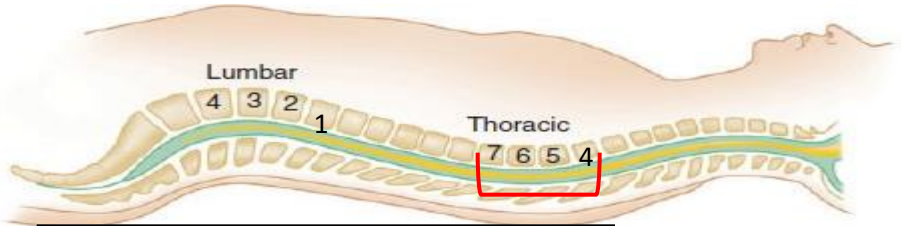
Reference: International PI UK. 2019

Bupibloc Heavy: Method of Administration

For Intrathecal Use Only



With the patient receiving the injection in the horizontal position and then turned supine



The blockade spreads to T4–T7 spinal segments

Reference: International PI UK. 2019

Bupibloc Heavy: Method of Administration

The recommended site of injection is below L3.

If the anesthesia appears inadequate, a change in patient position within twenty minutes of the injection may improve the distribution of the local anesthetic agent within the subarachnoid space e.g. Trendelenberg or right/left tilt.

If the anesthesia fails, a fresh attempt can be made to administer the anesthetic agent at a different level of the spinal cord, using a smaller volume of the medicinal product.

Reference: International PI UK. 2019

Bupibloc Heavy: Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to local anesthetics of the amide type.

General contraindications related to intrathecal anesthesia should be taken into account:

- Acute active diseases of the cerebrospinal system such as meningitis, tumours, poliomyelitis and cranial haemorrhage.
- Spinal stenosis and active disease (e.g. spondylitis, tuberculosis, tumour) or recent trauma (e.g. facture) in the vertebral column.
- Septicaemia.
- Pernicious anaemia with subacute combined degeneration of the spinal cord.
- Pyogenic infection of the skin at or adjacent to the site of puncture.
- Cardiogenic or hypovolaemic shock.
- Coagulation disorders or ongoing anti-coagulation treatment.

Bupibloc Heavy: Use in Special Population

Pregnancy

No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations.

However, note that the dose should be reduced by 20-30% for patients in the late stages of pregnancy due to the risk of neonatal respiratory depression, hypotension and bradycardia.

Bupivacaine transfers across to the placenta. Although the concentration of bupivacaine in the umbilical cord are lower than in the mother´s serum concentrations, the free bupivacaine concentrations will remain the same.

Breast-feeding

Bupivacaine enters in the mother's milk, but such small quantities that there is generally no risk of affecting the child at therapeutic dose levels.

Bupibloc Heavy: Adverse Effects

System Organ Class	Very Common (>1/10)	Common (>1/100, <1/10)
Cardiac disorders	Hypotension, bradycardia	
Gastrointestinal disorders	Nausea	Vomiting
Nervous system disorders		Postdural puncture headache
Renal and urinary disorders		Urinary retention, urinary incontinence
Musculoskeletal, connective tissue and bone disorders		
Immune system disorders		
Respiratory disorders		

Clinical Efficacy

Bupivacaine Heavy: Clinical Evidences

Standard preparation of bupivacaine contains glucose 80 mg/ml and produces extensive spread (thoracic) for most operations.

This is the range of block generally considered necessary for Caesarean section.[1]

Reference: 1. Br J Anaesth 2001; 86: 805±7.; 2. Anaesthesia 2018, 73, 499–511.

REVIEW ARTICLE I

Caesarean section

Review > Cochrane Database Syst Rev. 2013 May 31;(5):CD005143.
doi: 10.1002/14651858.CD005143.pub2.

Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section

Alex T Sia [1], Kelvin H Tan, Ban Leong Sng, Yvonne Lim, Edwin S Y Chan, Fahad Javaid Siddiqui

Abstract

Background: Bupivacaine is an amide local anaesthetic used in hyperbaric and isobaric forms. These are administered intrathecally into the spine to provide regional anaesthesia for caesarean section. Several trials have compared hyperbaric and isobaric bupivacaine but none have conclusively shown benefit of either.

Main results: We included six studies with a total of 394 patients in this review. Anaesthesia performed with hyperbaric bupivacaine appeared to be less likely to need conversion to general anaesthesia (two studies, 158 patients included in meta-analysis; RR 0.17, 95% confidence interval (CI) 0.03 to 0.94). There was no difference in the need for supplemental analgesics. The time till sensory block to the T4 level was also shorter with hyperbaric bupivacaine (two studies, 126 patients; MD -1.06 minutes, 95% CI -1.80 to -0.31). There were no other significant differences between the two anaesthetics.

Intrathecal hyperbaric bupivacaine had a more rapid onset of sensory blockade at the T4 level than isobaric bupivacaine. It may also result in less need for conversion to general anesthesia and supplemental analgesia.

Cochrane Database Syst Rev 2013 May 31;(5):CD005143.

REVIEW ARTICLE II

Caesarean section

Clinical Trial > Reg Anesth. Mar-Apr 1995;20(2):90-4.

Spinal anesthesia for cesarean delivery. A comparison of two doses of hyperbaric bupivacaine

C A De Simone [1], B L Leighton, M C Norris

Affiliations + expand

PMID: 7605770

Abstract

Background and objectives: Hyperbaric local anesthetic pools in the thoracic spinal curvature in supine patients. The authors hypothesized that patients receiving 12 or 15 mg of hyperbaric bupivacaine would achieve similar levels of sensory block but the spinal anesthetic would be denser and longer lasting in patients receiving the 15 mg dose.

Methods: Twenty eight healthy term parturients scheduled for elective cesarean delivery randomly received 12 or 15 mg hyperbaric 0.75% bupivacaine in 8.25% dextrose. Patients were in the right lateral position during drug injection and were then positioned supine with left uterine displacement on a horizontal operating table. A blinded anesthesiologist assessed the dermatome level of sensory analgesia to pinprick every 2 minutes for 20 minutes, then every 15 minutes until the sensory level regressed to T10.

Results: The mean level of sensory anesthesia was 2.2 spinal segments higher in patients receiving 15 mg versus 12 mg hyperbaric bupivacaine (24.8 +/- 3.7 versus 22.6 +/- 1.4 spinal segments; P = .031)

Parturients receiving 15 mg of hyperbaric bupivacaine developed a higher mean level and longer duration of sensory analgesia than those receiving 12 mg.

Reg Anesth. Mar-Apr 1995;20(2):90-4.

REVIEW ARTICLE III

Elective Caesarean section

Anaesthesia 2018, 73, 499–511 doi:10.1111/anae.14084

Review Article

2018

Hyperbaric vs. isobaric bupivacaine for spinal anaesthesia for elective caesarean section: a Cochrane systematic review

B. L. Sng,[1,2] N. L. R. Han,[5] W. L. Leong,[3] R. Sultana,[7] F. J. Siddiqui,[8] P. N. Assam,[9] E. S. Chan,[10] K. H. Tan[6] and A. T. Sia[1,4]

Summary

Both isobaric and hyperbaric bupivacaine have been used for spinal anaesthesia for elective caesarean section, but it is not clear if one is better than the other. The primary objective of this systematic review was to determine the effectiveness and safety of hyperbaric bupivacaine compared with isobaric bupivacaine administered during spinal anaesthesia for elective caesarean section. We included 10 studies with 614 subjects in the analysis. There was no evidence of differences either in the risk of conversion to general anaesthesia, with a relative risk (95%CI) of 0.33 (0.09–1.17)) being 0.61 (0.26– edrine, the amount reach a sensory block height of T4, with a mean difference (95%CI) of −1.06 min (−1.80 to −0.31). Due to the rarity of some outcomes, dose variability, use of adjuvant drugs and spinal technique used, future clinical trials should look into using adequate sample size to investigate the primary outcome of the need for supplemental analgesia.

Hyperbaric bupivacaine took less time to reach a sensory block height of T4, with a mean difference of -1.06 min.

Anaesthesia 2018, 73, 499–511.

CLINICAL TRIAL

Major gynaecological procedures

Br. J. Anaesth. (1981), 53, 279

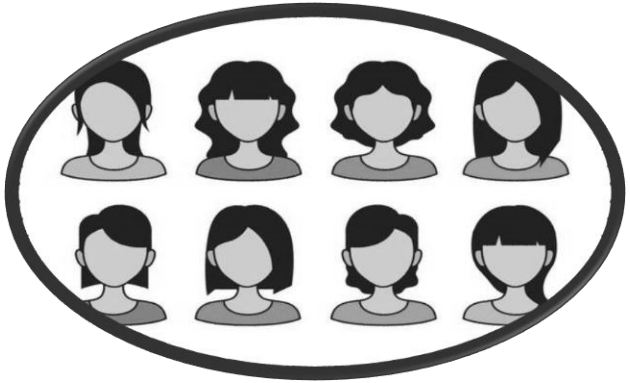
EFFECT OF BARICITY ON SPINAL ANAESTHESIA WITH BUPIVACAINE

W. A. CHAMBERS, H. H. EDSTROM AND D. B. SCOTT

SUMMARY

In a double-blind study of spinal anaesthesia with 0.5% bupivacaine 3 ml with no glucose, 5% glucose or 8% glucose all three solutions gave consistently good nerve blocks. The hyperbaric solutions (5% and 8% glucose) produced a greater cephalad spread and were suitable for lower abdominal surgery, whereas the plain solution (no glucose) seldom affected the thoracic nerves. Cardiovascular changes were more marked with the hyperbaric solutions but only necessitated treatment on two occasions. The duration of block was not affected by baricity and was in the range 140–160 min.

Clinical Trial: Study Groups



N= 30 female patients aged 18—65 yr

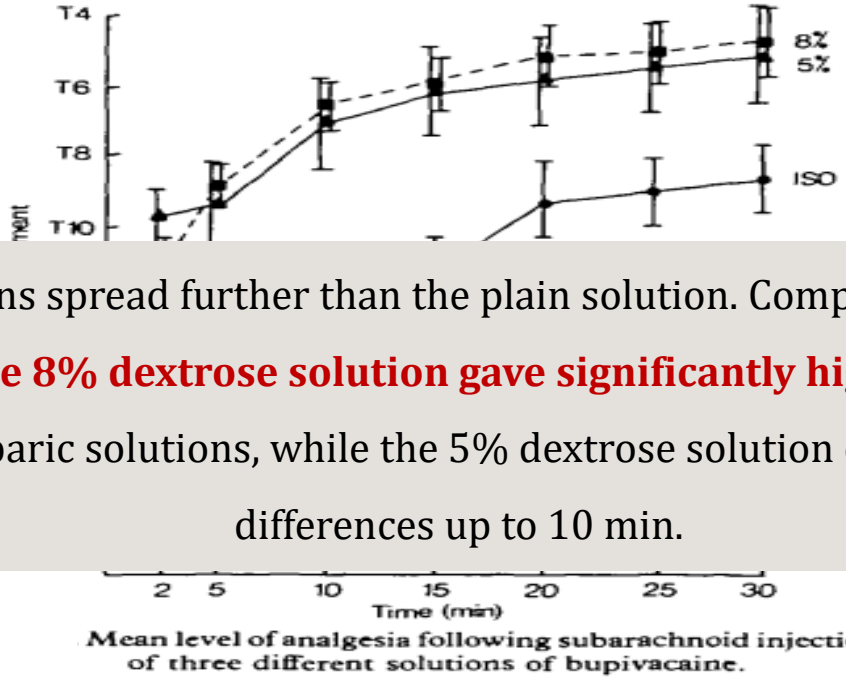
Bupivacaine 0.5% was used throughout.

One of the hyperbaric solutions contained 5% dextrose (sp. gr. 1.018 at 20 °C) and t**he other 8% dextrose** (sp. gr. 1.026 at 20 °C).

The plain solution, although presented in special ampoules, was the same as that currently supplied for extradural administration. That solution is slightly hyperbaric (sp. gr. 1.004) at 20 °C and slightly hypobaric (sp. gr. 0.997) at 37 °C.

Br. J. Anaesth. (1981), 53, 279

Clinical Trial: Results



Mean level of analgesia following subarachnoid injection of three different solutions of bupivacaine.

The hyperbaric solutions spread further than the plain solution. Comparing anesthesia at each of the time intervals, **the 8% dextrose solution gave significantly higher blocks at all times** compared with isobaric solutions, while the 5% dextrose solution only showed significant differences up to 10 min.

Br. J. Anaesth. (1981), 53, 279

Summary

- Bupivacaine Heavy is indicated in adults and children of all ages for intrathecal (subarachnoid) spinal anesthesia for surgery.[1]
- The hyperbaric solutions (8% glucose) produced a greater spread and were suitable for lower abdominal surgery.[2]
- In caesarean section hyperbaric bupivacaine took less time to reach a sensory block of T4.[3]
- Patients receiving 15 mg of hyperbaric bupivacaine developed a higher mean level and longer duration of sensory analgesia.[4]

Reference: 1. CDSCO , as accessed on 7th Feb 2022- https://cdscoonline.gov.in/CDSCO/Drugs
; 2. Br. J. Anaesth. (1981), 53, 279; 3. Anaesthesia 2018, 73, 499–511.; 4. Reg Anesth. Mar-Apr 1995;20(2):90-4.

THANK YOU !

℞ DEXMEDINE

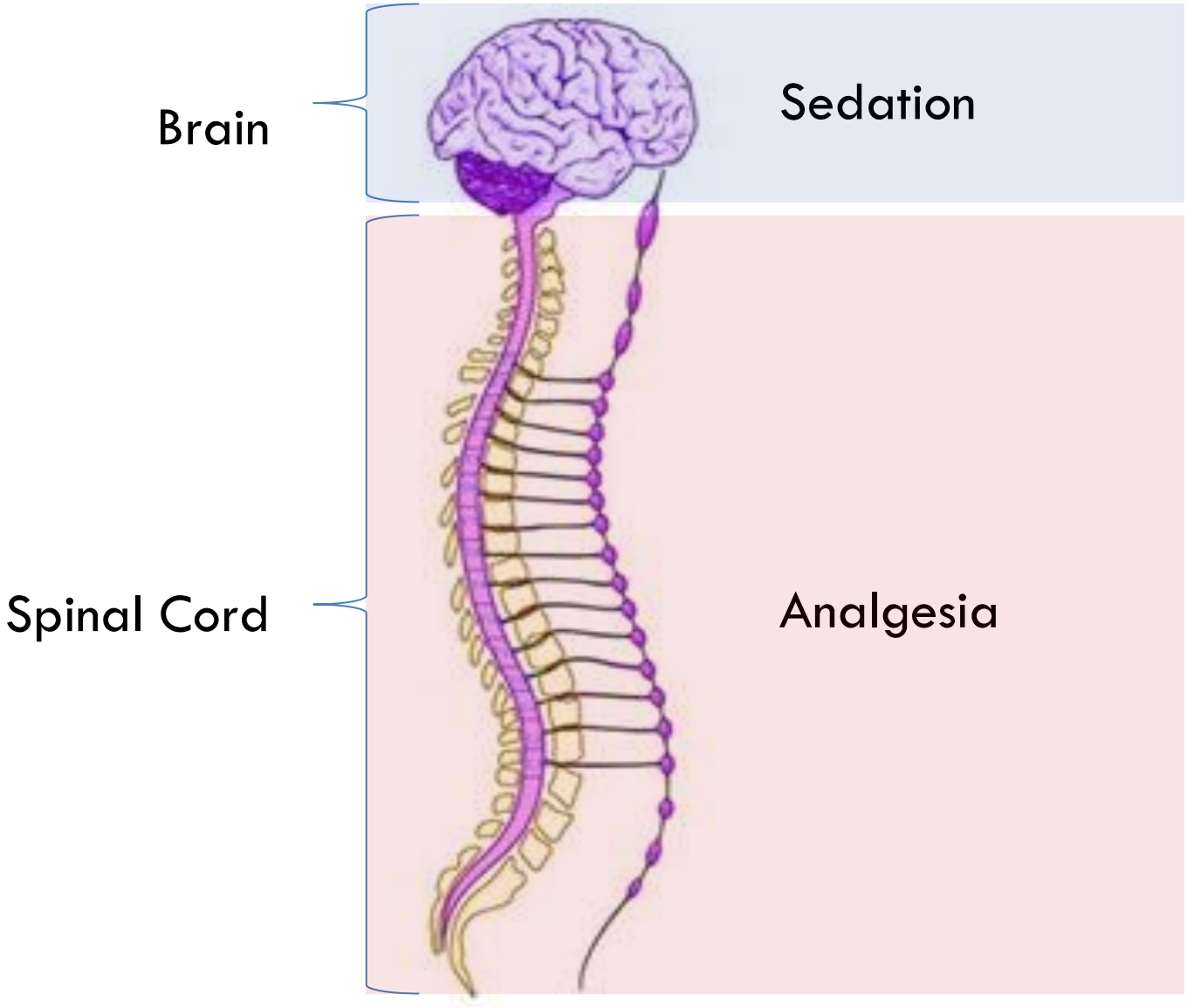
Inj. Dexmedetomidine HCl 50mcg/0.5ml, 100mcg/1ml, 200mcg/2ml

Product Introduction

DESCRIPTION:

- Dexmedine, Highly selective α_2 adrenergic receptor agonist
- Approved by USFDA in Dec 1999 for ICU sedation
- And in 2008 for procedural sedation

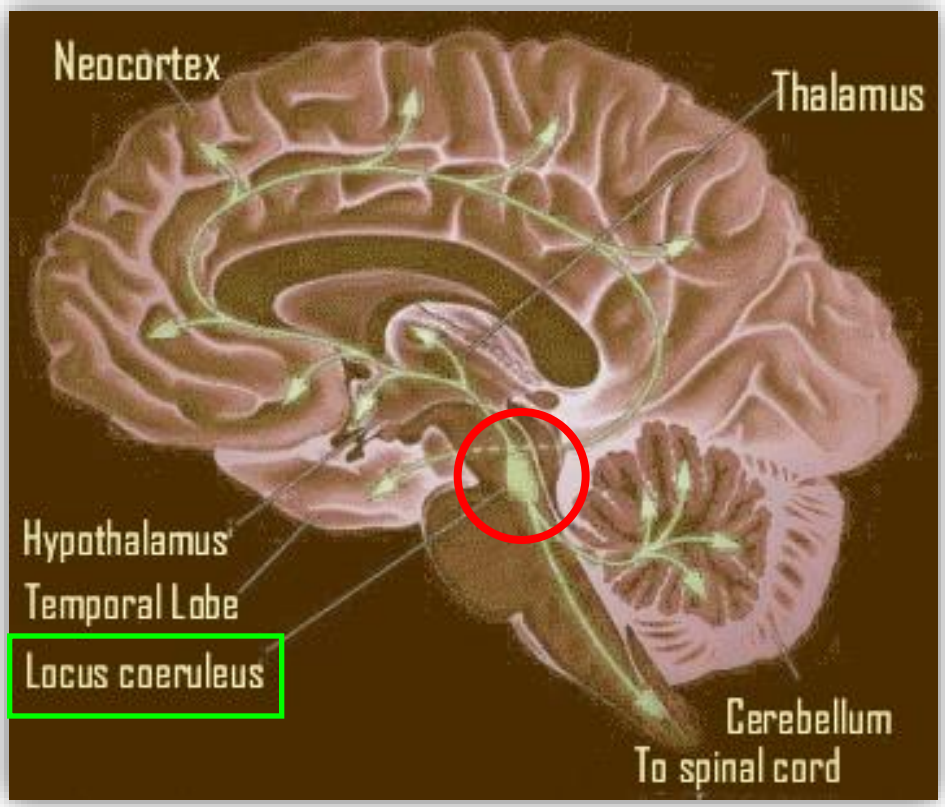
Mechanism of action



Locus Ceruleus (LC)

- Major site of noradrenergic innervations in the brain

- Involved in function like Anxiety, Arousal, Sleep



Drugs 2011; 71 (11): 1481-1501

Action at Locus Ceruleus (LC)

Dexmedetomidine (α_2 agonist)

↓

Activates potassium channels

↓

Hyperpolarization

↓

Suppression of Neuronal activity

↓

Inhibition of NA release (LC)

↓

↓ firing from LC

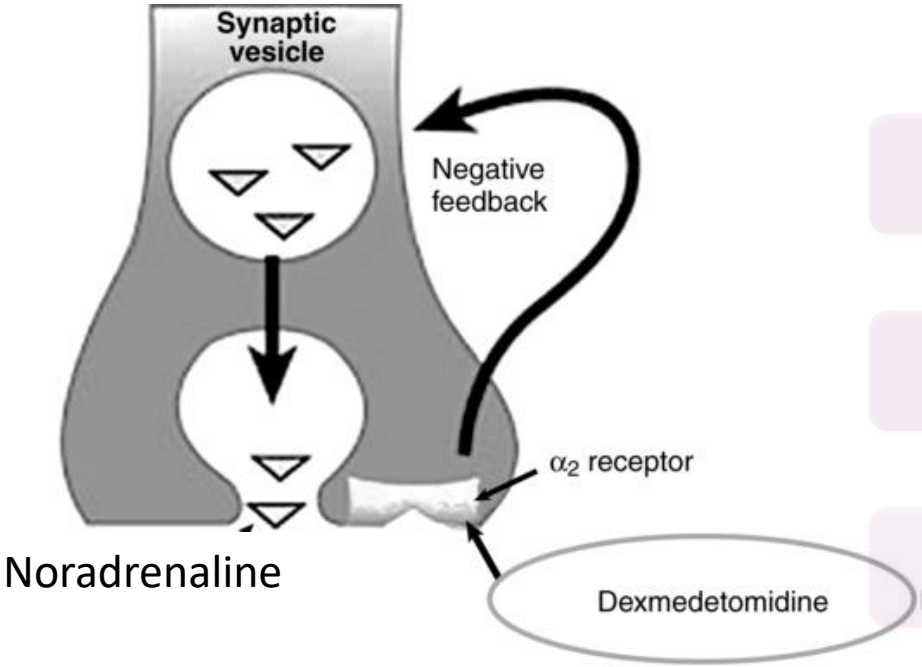
↓

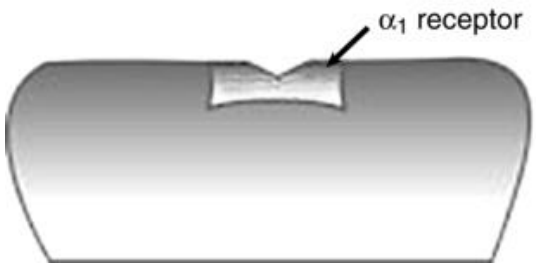
Sedation

Induces a form of sedation resembling natural sleep from which the pt is easily and quickly aroused

Adapted from Drugs 2011; 71 (11): 1481-1501 and Drugs. 2015 Jul;75(10)1119-30

Action at Locus Ceruleus (LC)





Inhibition of NA release (LC)

↓ firing from LC

Sedation

Induces a form of sedation resembling natural sleep from which the pt is easily and quickly aroused

Action at Spinal Cord

Dexmedetomidine (α_2 agonist)

↓

Activates α2-C receptors

↓

↓ release of Substance P and Glutamate

↓

Analgesia

J Anaesthesiol Clin Pharmacol. 2011 Jul-Sep; 27(3): 297–302.

Selectivity to alpha receptors

- Alpha$_2$ selectivity is 8 times greater than Clonidine[2]

More effective than clonidine for sedation and analgesia[3]

- Also binds to Imidazoline receptors[1]

1Drugs. 2015 Jul;75(10)1119-30. 2Drugs. 2000 Feb;59(2)263-8 3Rev Bras Anestesiol 2012; 62: 1: 118-133

Pharmacokinetics

- Follows **linear pharmacokinetics**
- Rapidly distributed, and **onset of action- @15 minutes***
- **Tmax – 1hr, Half life – 1.5 hrs**
- No accumulation with continued administration for up to 14 days
- Undergoes extensive hepatic metabolism
- Predominantly excreted in urine

Indication

Intensive Care Unit Sedation

For sedation of initially intubated and mechanically ventilated patients in ICU

Should be administered by continuous infusion not to exceed 24 hours.

Procedural Sedation

For sedation of non-intubated patients prior to or during surgical procedures.

Haemodynamic effect

1. Initial stimulation of alpha 2b receptors → ↑ BP

Can be decreased by slow infusion and avoiding of loading dose

2. ↓ BP & HR due to inhibition of Central sympathetic outflow

Dose Dependent

↓

Cardiovascular effects are PREDICTABLE

3. No rebound hypertension/tachycardia*

Rev Bras Anestesiol 2012; 62: 1: 118-133 *Drugs 2011; 71 (11): 1481-1501 & Drugs. 2015 Jul;75(10)1119-30

Cardioprotection

Studies has shown hemodynamic stabilization leading to cardioprotective action

Rev Bras Anestesiol 2012; 62: 1: 118-133

Target Customers

- Anaesthesiologist
- Intensivist

Dosage

Initiation of ICU Sedation	**For adult patients:** a loading infusion of 1 mcg/kg over 10 **minutes.** **For adult patients being converted from alternate sedative therapy:** a loading dose may not be required **For patients over 65 years of age:** Reduce the dose **For adult patients with impaired hepatic-function**: Reduce the dose
Maintenance of ICU Sedation	**For adult patients:** a maintenance infusion of 0.2 to 0.7 mcg/kg/**hour.** **For patients over 65 years of age:** Reduce the dose **For adult patients with impaired hepatic function**: Reduce the dose

Initiation of Procedural Sedation	**For adult patients:** a loading infusion of 1 mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation in adult patients:** a loading infusion of one mcg/kg over 10 **minutes**. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 **minutes** **For adult patients with impaired hepatic function**: a dose reduction should be considered
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/**hour** and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/**hour**. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation in adult patients:** a maintenance infusion of 0.7 mcg/kg/**hour** is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered **For adult patients with impaired hepatic function:**a dose reduction should be considered

Renal impairment

Unlike midazolam and propofol,

NO dose adjustment in renal impairment pts

Highlighting benefits over other preferred molecules

Propofol

Propofol is a respiratory and cardiovascular depressant

Propofol has direct cardio depressant effects, leading to decreased blood pressure and heart rate.

Highlighting benefits over other preferred molecules

Midazolam

Compared to midazolam, dexmedetomidine was similarly effective for sedation, but shortened the time to extubation.

Midazolam is a respiratory and cardiovascular depressant

Midazolam has no analgesic properties.

Highlighting benefits over other preferred molecules

Etomidate

Etomidate has been shown to depress adrenal cortical function in critically ill patients. Neither titration nor continuous infusion is recommended.

The **adrenal cortex** produces numerous hormones called corticosteroids, which are involved in important **functions** of the body such as regulation of metabolism, blood pressure, and sodium and potassium levels.

Highlighting benefits over other preferred molecules

Fentanyl

Fentanyl may produce more prolonged respiratory depression than other opioid analgesics. Also cause nausea, vomiting

Highlighting benefits over other preferred molecules

Clonidine

May cause low blood pressure and long recovery time ,

discontinuation results in rebound effect

Why Dexmedetomidine?

Dexmedetomidine has become one of the frequently used drugs in anesthetic armamentarium, along with routine anesthetic drugs, due to its

- **Hemodynamic stability**
- **No respiratory depression**
- **Sedative action**
- **Anxiolytic action**
- **Analgesic effect**
- **Cardio protective & Neuro protective**
- **Reno Protective**
- **Anesthetic sparing effects**

Sudheesh K, Harsoor S S. Dexmedetomidine in anaesthesia practice: A wonder drug?. Indian J Anaesth 2011;55:323-4

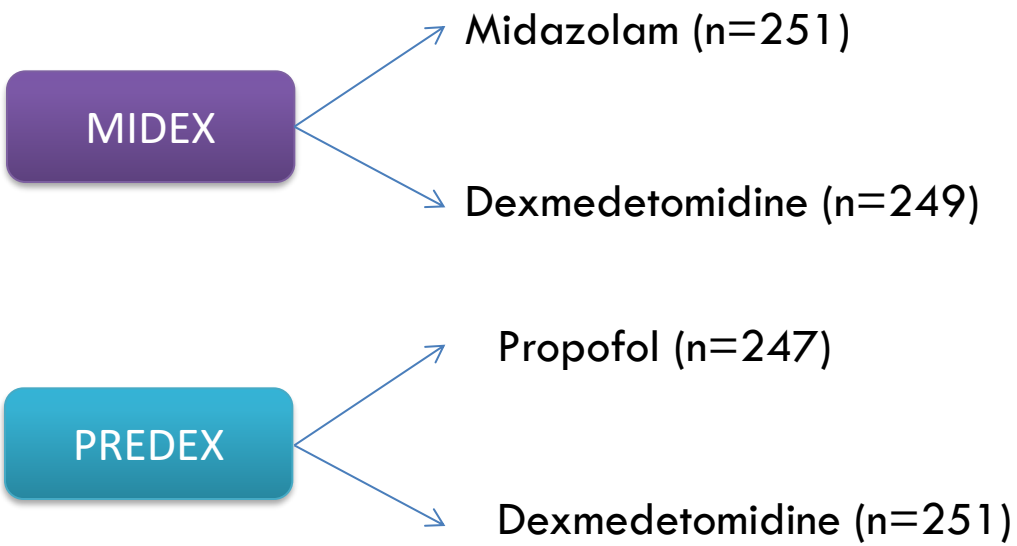
Clinical Evidence

in ICU sedation

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

Two phase 3 multicentre, randomized, double-blind trials carried out from 2007 to 2010.



JAMA. 2012;307(11):1151-1160

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

	Vs propofol			*Vs* midazolam		
	Dexmed	**Propofol**	**Result**	**Dexmed**	**Midazolam**	**Result**
Median duration of mechanical ventilation (hours)	97	118	NS	123	164	p=0.03
Median time to extubation (hours)	69	93	p=0.04	101	147	p=0.01
Median length of stay (hours)	164	185	NS	211	243	NS

NS=not significant

Table 3. Primary and secondary outcomes from the key efficacy trials of dexmedetomidine (dexmed) *vs* propofol and midazolam[10]

JAMA. 2012;307(11):1151-1160

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Two Randomized Controlled Trials

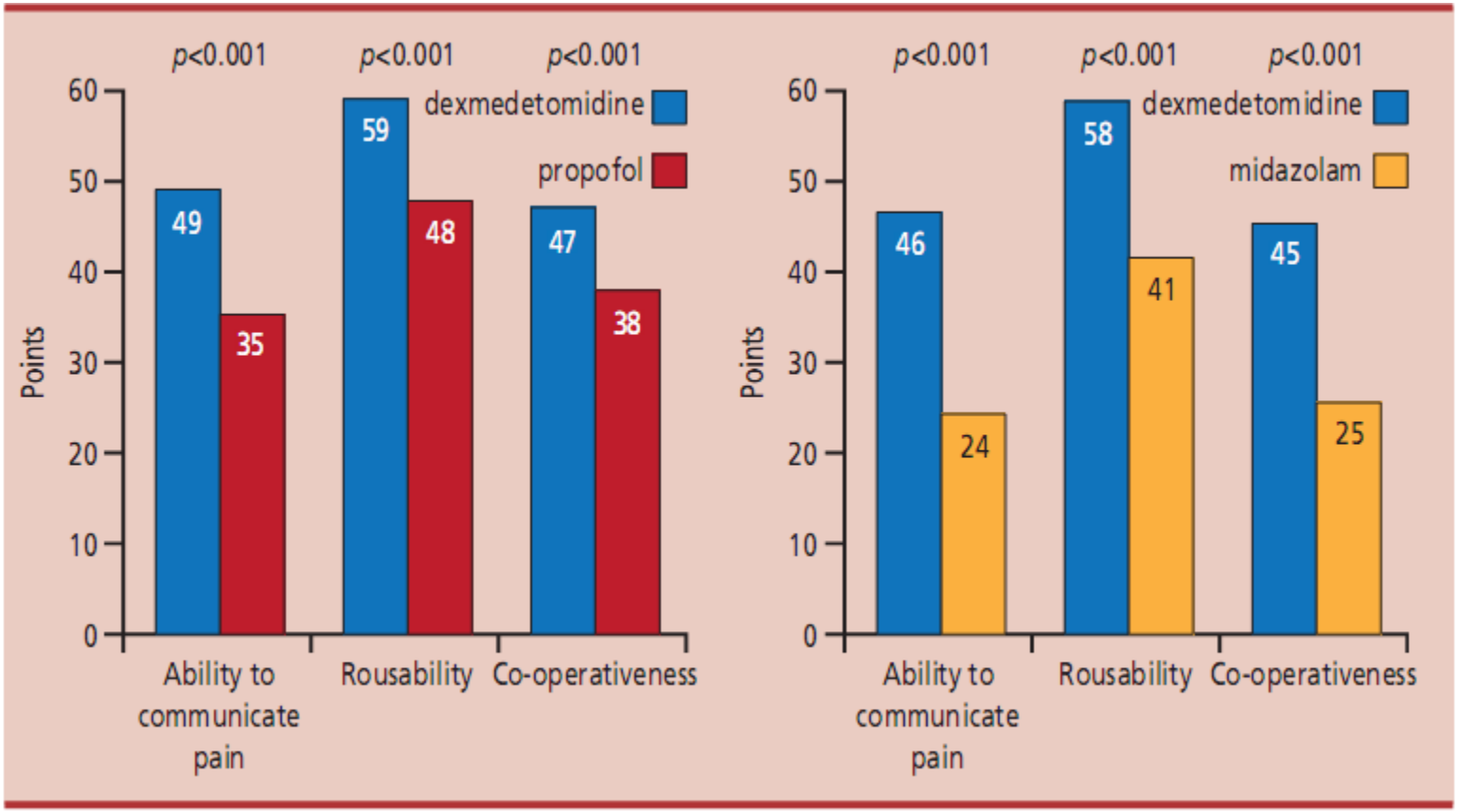


Figure 2. Nurse assessments of patients' ability to communicate, rousability and co-operativeness using a visual analogue scale[10]

JAMA. 2012;307(11):1151-1160

CONCLUSIONS:

Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam and improved patients' ability to communicate pain compared with midazolam and propofol.

Comparison of clonidine and dexmedetomidine for short-term sedation of intensive care unit patients

S N Medical College, Agra

70 patients either received

IV clonidine (1 µg/kg/h titrated up to 2 µg/kg/h to attain target sedation) OR

IV dexmedetomidine (loading 0.7 µg/kg and maintenance 0.2-0.7 µg/kg/h

Conclusion:

Both clonidine and dexmedetomidine produced effective sedation; however, the hemodynamic stability provided by dexmedetomidine gives it an edge over clonidine for short-term sedation of ICU patients.

Indian J Crit Care Med. 2014 Jul; 18(7): 431–436.

Clinical Evidence

in ortho

Study 1

Comparative study of dexmedetomidine and fentanyl as an adjuvant to epidural bupivacaine for postoperative pain relief in adult patients undergoing total knee replacement: a randomized study

Gian Sagar Medical College and Hospital, Ram Nagar, Banur, Punjab, India

N=460

Group D: Dexmedetomidine 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml and infused epidurally at a rate of 5ml/hr for the postoperative 72 hours.

Group F : Fentanyl 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml and infused epidurally at a rate of 5ml/hr for the postoperative 72 hours

Journal of Anesthesiology & Clinical Science
ISSN 2049-9752 | Volume 5 | Article 1

Study 1

Comparative study of dexmedetomidine and fentanyl as an adjuvant to epidural bupivacaine for postoperative pain relief in adult patients undergoing total knee replacement: a randomized study

In Dexmedetodine group

- **Better quality of analgesia**
- **Lower requirement for opioids**
- **Sedation was significantly higher**
- **Lower incidence of respiratory depression**

Journal of Anesthesiology & Clinical Science
ISSN 2049-9752 | Volume 5 | Article 1

Clinical Evidence

in cardiac patients

Dexmedetomidine Vs Propofol

Propofol-Based Versus Dexmedetomidine-Based Sedation in Cardiac Surgery Patients

582 pts (≥18 years) of age who received propofol-based or dexmedetomidine-based sedation after cardiac valve or (CABG) surgery

	Dexmedetomidine (n = 291)	Propofol (n = 291)	p value
Early Extubation	200 (68.7%)	169 (58.1%)	0.008
Time to Extubation (h)	8.8	12.8	0.026
ICU stay (h)	43.9	52.5	0.067
Hospital stay (h)	181.9	221.3	0.001

J Cardiothorac Vasc Anesth. 2013 Dec;27(6)1289-94.

Post-op Delirium

Dexmedetomidine *versus* Propofol Sedation Reduces Delirium after Cardiac Surgery

A Randomized Controlled Trial

(ANESTHESIOLOGY 2016; 124:362-8)

- The incidence of postoperative delirium in patients undergoing cardiac surgery has been reported in a range of 20 to 50% with elderly patients being at the greatest risk

Post-op Delirium

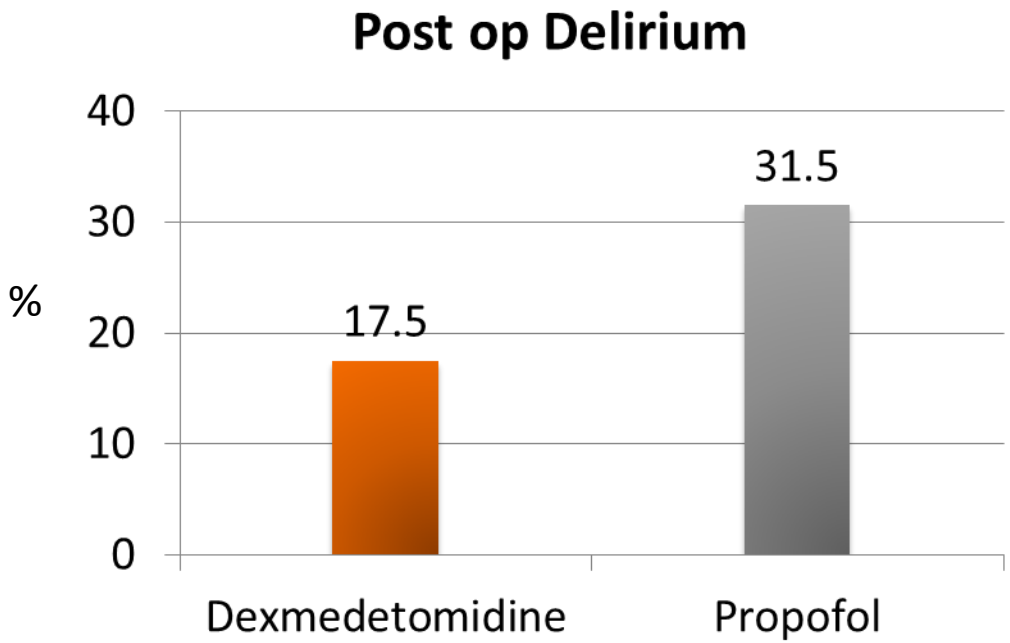


Table 2. Onset and Duration of Delirium and the Length of Stay in Patients with Delirium

	Dexmedetomidine Group (n = 16)	Propofol Group (n = 29)	*P* Value
Onset of delirium, d, median (range)	2 (1–4)	1 (1–4)	0.027
Duration of delirium, d, median (range)	2 (1–4)	3 (1–5)	0.04
Extubation time, h, median (range)	5.5 (3.5–14.2)	7.6 (3.8–202.2)	0.0007
Intensive care unit length of stay, h, median (range)	67.8 (20–214)	76.5 (17.8–956.5)	0.38
Hospital length of stay, d, median (range)	7.5 (5–32)	10 (6–74)	0.054

(ANESTHESIOLOGY 2016; 124:362-8)

Atrial Fibrillation

RESEARCH Open Access

Dexmedetomidine sedation reduces atrial fibrillation after cardiac surgery compared to propofol: a randomized controlled trial

After successful CPB (n=90) pts were equally divided into 2 groups

Dexmedetomidine or propofol was continuously infused without a loading dose.

The intravenous infusion speed of dexmedetomidine (≤1.5 μg/kg/h) or propofol (≤3 mg/kg/h) was adjusted to maintain RASS values between 0 and -3

The infusion of the sedative was stopped before extubation at the discretion of the attending physicians

Liu *et al. Critical Care* (2016) 20:298

Atrial Fibrillation

RESEARCH Open Access

Dexmedetomidine sedation reduces atrial fibrillation after cardiac surgery compared to propofol: a randomized controlled trial

- Dexmedetomidine sedation reduced new-onset postoperative AF and shortened the ICU stay in patients after cardiac surgery compared to propofol sedation
- The administration of dexmedetomidine during the early postoperative period could prevent one case of AF for every five patients undergoing cardiac surgery

Liu *et al. Critical Care* (2016) 20:298

Clinical Evidence

in neuro-surgery

Head injury

84 pts with TBI (Glasgow scale 7 to 8), mean age 44 received either propofol or dexmedetomidine during mechanical ventilation

IV propofol infusion at a dose of 4 to 12 mg/kg/hour. OR
IV infusion of dexmedetomidine at a dose of 0.2 to 1.4 mg/kg/hour.

Conclusion

Go to:

Using dexmedetomidine at a dose of 0.2 to 1.4 mg/kg/hour for intravenous sedation is safe in terms of hemodynamic stability and blood oxygenation for sedation during mechanical lung ventilation in traumatic brain injury patients.

Crit Care. 2014; 18(Suppl 1): P416.

Clinical Evidence

IN GYNAC

Caesarean section

Dexmedetomidine improves intraoperative conditions and quality of postoperative analgesia when added to epidural in elective cesarean section

N= 50

Either 10 mL 0.25% plain bupivacaine plus fentanyl 100 mcg in 10 mL 0.9% sodium chloride (BF group) or
10 mL 0.25% plain bupivacaine plus mixture of fentanyl 100 mcg and dexmedetomidine 1 mcg/kg in 10 mL 0.9% sodium chloride (DBF group).

Conclusion: Adding dexmedetomidine to regular mixture of epidural anesthetics in women undergoing elective cesarean section improved intraoperative conditions and quality of postoperative analgesia without maternal or neonatal significant side effects.

Egyptian Journal of Anaesthesia (2014) **30**, 353–357

Hysterectomy

Comparison of Effects of Adding Dexmedetomidine as an Adjuvant to Intrathecal 0.5% Bupivacaine versus Fentanyl in Gynaecological Procedures

Government Medical College, Nagpur, Maharashtra

76 pts (30-60 yrs undergoing vaginal hysterectomy and vaginal wall repair under GA)
Group I received 15mg of 0.5% bupivacaine and 25ugm of fentanyl
Group II received 15mg of 0.5% bupivacaine and 5ugms of dexmedetomidine

Conclusion: The 5 µg dexmedetomidine seem to be an attractive alternative to 25 µg Fentanyl as an adjuvant to spinal bupivacaine in vaginal hysterectomy patients.

Research Chronicle in health sciences 2015,1(4),206-212

Hysterectomy

Comparison between Dexmedetomidine and Clonidine as an Adjuvant to Spinal Anesthesia in Abdominal Hysterectomy

Dhiraj General Hospital, Piparia, Vadodara

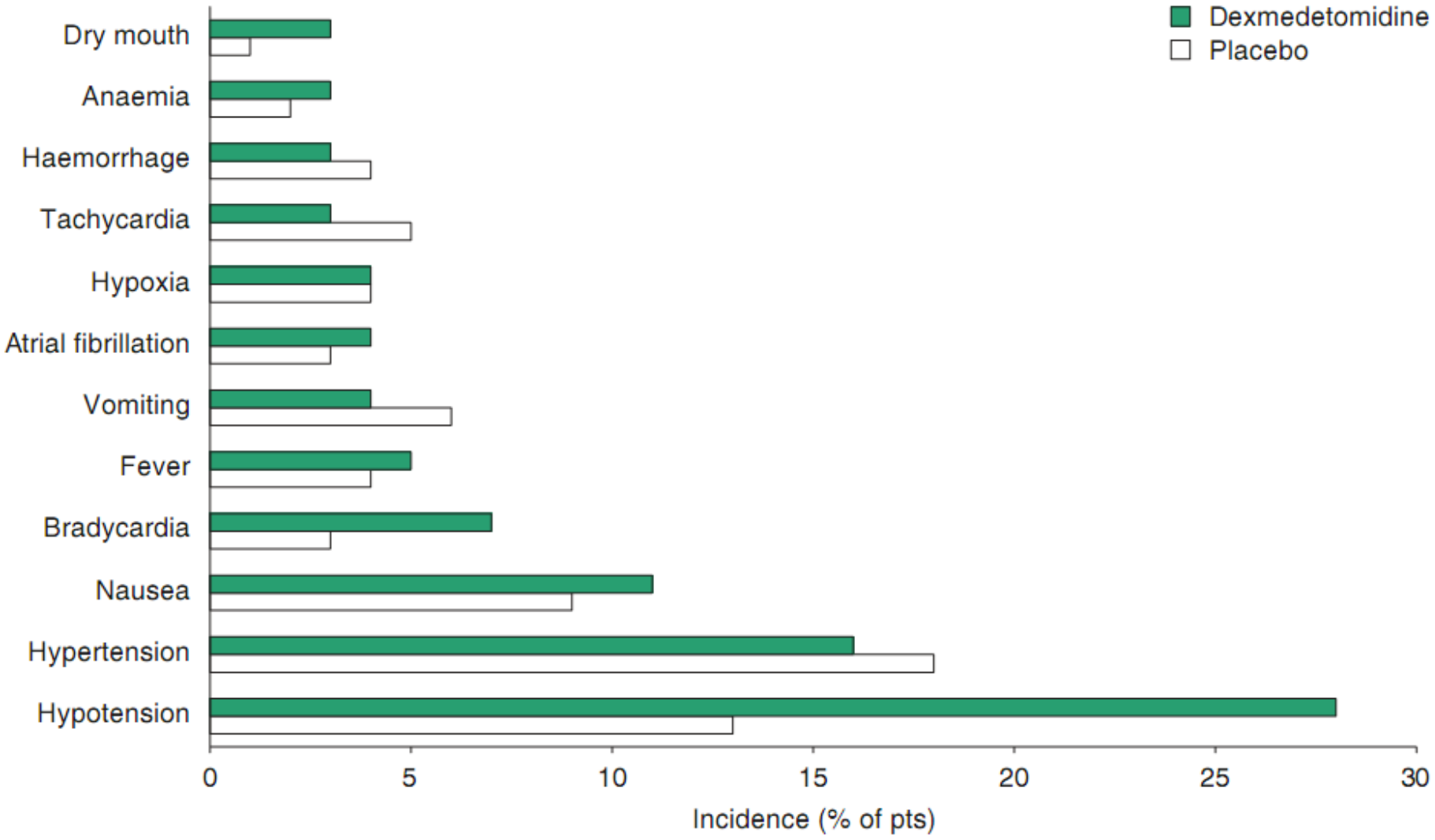
60 pts (30-60 yrs)

All patients received hyperbaric bupivacaine 0.5% (heavy) 15 mg intrathecally with dexmedetomidine 10 µg and with clonidine 15 µg respectively (30 each).

It can be concluded that though both clonidine and dexmedetomidine prolonged duration of sensory and motor block of bupivacaine, dexmedetomidine is better in terms of longer duration of action.

International Journal of Science and Research (IJSR). 2015 Volume 4 Issue 1

Adverse Effect Profile



Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Uncontrolled hypotension

Pregnancy & Lactation

Pregnancy Category C

There are no adequate and well-controlled studies of Dexmedetomidine use in pregnant women

Lactation

Caution should be exercised when Dexmedetomidine is administered to a nursing woman.


Future of
Dexmedetomidine

Paediatric

Dexmedetomidine for Sedation in the Pediatric Intensive Care

Marcia L. Buck, PharmD, FCCP
Pediatr Pharm. 2006;12(1)

Recommended adult dosage range of 0.2 to 0.7 mcg/kg/hr may also be used in children

Many paediatric centres are reducing or omitting the loading dose in an effort to avoid cardiovascular instability

Summary

Dexmedetomidine offers an additional choice for the sedation of children receiving mechanical ventilation or requiring procedural sedation. It may be particularly useful in children with underlying neurologic disorders, who often develop agitation or adverse hemodynamic and respiratory effects with opioids or benzodiazepines.

Paediatric

Comparison of dexmedetomidine versus propofol for maintenance of anesthesia during invasive procedures in pediatric oncology patients: a controlled randomized double-blind study

40 children (6-12 yrs), ASA I or II with hematological cancer

All patients received ketamine0.5 mg/kg intravenously before the start of procedure

In group A, propofol infusion was started at a rate of 2 mg/kg over 10 min then the infusion rate of 50 µg/kg/min was adjusted until patient fall asleep and reach a sedation score 5–6 according to the Ramsay sedation score

In group B, dexmedetomidine infusion was started at a rate of 0.5 µg/kg, intravenous, for 10 min, and this was based on doses used during ICU sedation

Ain-Shams Journal of Anesthesiology 2014, 07:163–169

Paediatric

Comparison of dexmedetomidine versus propofol for maintenance of anesthesia during invasive procedures in pediatric oncology patients: a controlled randomized double-blind study

Conclusion

Dexmedetomidine/ketamine infusion provides hemodynamic stability, lower recovery excitation, and pain scores, although recovery time is prolonged when compared with propofol/ketamine infusion in invasive procedures in pediatric oncology patients. Thus, it represents an alternative sedoanalgesic choice for this population.

Ain-Shams Journal of Anesthesiology 2014, 07:163–169

Urology

Dexmedetomidine versus clonidine as an adjunct to intrathecal small dose ropivacaine in patients undergoing transurethral resection of prostate

Intrathecal dexmedetomidine with ropivacaine provides faster onset, better operating conditions, and patient comfort in patients undergoing TURP.

Group I patients received 1 ml isobaric ropivacaine 0.75% + 15 µg clonidine
Group II patients received 1 ml isobaric ropivacaine 0.75% + 5 µg dexmedetomidine

Ain-Shams Journal of Anesthesiology 2014, 07:534–538

Dental

A comparison of dexmedetomidine and midazolam for sedation in third molar surgery

Dexmedetomidine produces comparable sedation to midazolam with less amnesia and reduced pt movement.

Either dexmedetomidine 1 µg/kg (Group D) or midazolam 5 mg (Group M) was mixed with normal saline to a total volume of 20 mL

Anaesthesia (Oxford), 2007, v. 62 n. 11, p. 1132-1138

ENT & Ophthalmology

International Journal of Basic & Clinical Pharmacology. 2013;2(5)562-566

A comparative study of dexmedetomidine vs midazolam for sedation and hemodynamic changes during tympanoplasty and modified radical mastoidectomy

Journal of Anaesthesiology Clinical Pharmacology | April-June 2013 | Vol 29 | Issue 2

A prospective randomized double-blind study comparing dexmedetomidine vs. combination of midazolam-fentanyl for tympanoplasty surgery under monitored anesthesia care

Saudi Journal of Anesthesia Vol. 5, Issue 1, January-March 2011

Dexmedetomidine versus propofol for sedation in patients undergoing vitreoretinal surgery under sub-Tenon's anesthesia

Highlights

- A potent, highly selective α-2 adrenoceptor agonist
- Sedative, analgesic, anxiolytic, and opioid-sparing properties
- Provides a unique type of sedation, "conscious sedation"
- Quick onset and a relatively short duration of action
- Minimal respiratory depression with Cardioprotection and Neuroprotection

In procedural sedation & maintenance of ICU sedation

Rx DEXMEDINE

INTRODUCING

Inj. Dexmedetomidine HCl 50mcg/0.5ml, 100mcg/1ml, 200mcg/2ml

Puts ICU bills on diet

An opioid sparing novel sedative-analgesic

- Analgesic need reduced by 50%[1]
- Safety persist beyond 24 hours[1]
- Easily arousal sedation attained[2]
- No respiratory depression[1]

Recommended by - Society of Critical Care Medicine[3]

MIDFAST

Midazolam Inj. 5mg/ml, 5mg/5ml &10mg/10ml

Product Introduction

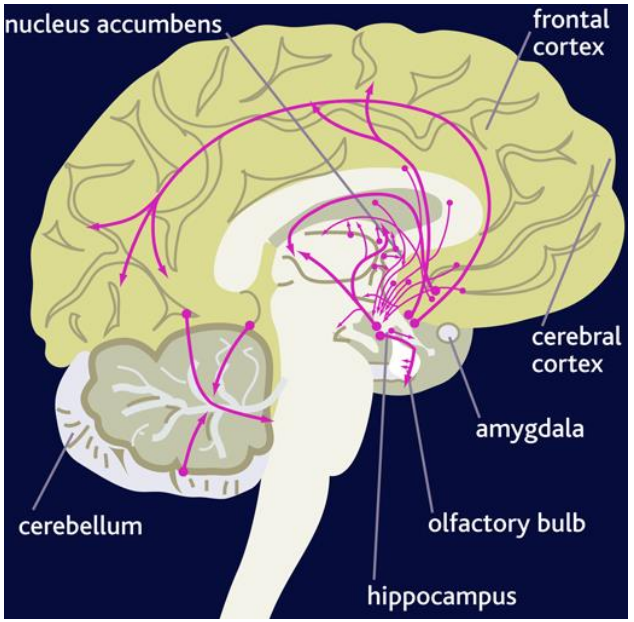
DESCRIPTION:

- MIDFAST (Midazolam) is a short-acting benzodiazepine central nervous system (CNS) depressant
- It is used for inducing sedation and amnesia before medical procedures

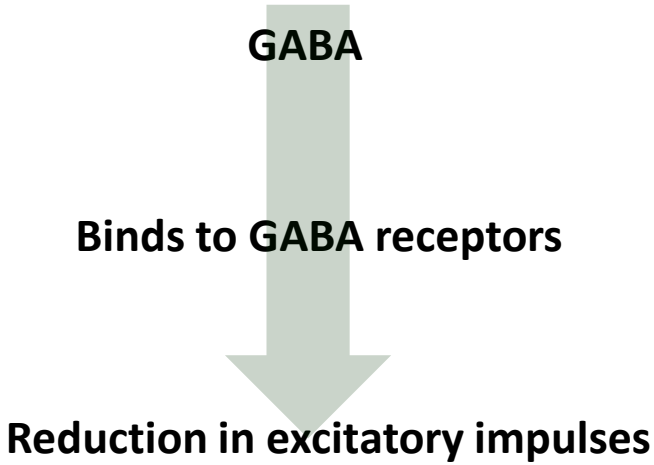
GABA (gamma-Amino Butyric acid)

- GABA, a neurotransmitter, is found in 30-40% of all synapses in the CNS

- GABA controls the fear or anxiety when neurons are overexcited



GABA (gamma-Amino Butyric acid**)**



How Midazolam acts?

MIDAZOLAM

↓

GABA receptor agonist

↓

Activates GABA receptors

↓

Reduction in excitatory impulses

↓

Relaxes the patient, Sedation

Pharmacokinetics

Bioavailability	IV- 100%, intramuscular >90%
Protein binding	97%
Metabolism	Liver
Onset of action	within 5 min (IV), 15 min (IM),
Biological half-life	1.5-2.5 hours
Duration of action	1 to 6 hrs
Excretion	Kidney

Indication

- For surgical sedation
- Sedation in mechanical ventilation

Target Customers

- Anaesthesiologist
- Intensivist

Dosage

Indication	Adults < 60 y	Adults 60 y / debilitated or chronically ill	Children
Conscious sedation	***i.v.*** Initial dose: 2 - 2.5mg Titration doses: 1mg Total dose: 3.5 - 7.5mg	***i.v*** Initial dose: 0.5 - 1mg Titration doses: 0.5 - 1mg Total dose: < 3.5mg	***i.v. in patients 6 months - 5 years*** Initial dose: 0.05 - 0.1mg/kg Total dose: < 6mg ***i.v. in patients 6-12 years*** Initial dose: 0.025 - 0.05mg/kg Total dose: < 10mg ***rectal > 6 months*** 0.3 - 0.5mg/kg ***i.m. 1 - 15 years*** 0.05 - 0.15mg/kg

https://www.medicines.org.uk/emc/product/3605/smpc

Indication	Adults < 60 y	Adults 60 y / debilitated or chronically ill	Children
Anaesthesia premedication	***i.v.*** 1-2mg repeated ***i.m.*** 0.07 - 0.1mg/kg	***i.v.*** Initial dosage: 0.5mg Slow uptitration as needed ***i.m.*** 0.025 - 0.05mg/kg	***rectal > 6 months*** 0.3 - 0.5mg/kg ***i.m. 1 - 15 years*** 0.08 - 0.2mg/kg
Anaesthesia induction	***i.v.*** 0.15 - 0.2mg/kg (0.3 -0.35 without premedication)	***i.v.*** 0.05 - 0.15g/kg (0.15 -0.3 without premedication)	
Sedative component in combined anaesthesia	***i.v.*** intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 -0.1mg/kg/h	***i.v.*** lower doses than recommended for adults < 60 years	

https://www.medicines.org.uk/emc/product/3605/smpc

	Adults	Pedia
Sedation in ICU	***i.v.*** Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5mg Maintenance dose: 0.03 - 0.2mg/kg/h	***i.v. in neonates ≤ 32 weeks gestational age*** 0.03mg/kg/h ***i.v in neonates > 32 weeks and children up to 6 months*** 0.06mg/kg/h ***i.v. in patients > 6 months of age*** Loading dose: 0.05 - 0.2mg/kg Maintenance dose: 0.06 - 0.12mg/kg/h

https://www.medicines.org.uk/emc/product/3605/smpc

For surgical sedation & sedation
in mechanical ventilation

Rx MIDFAST

Inj. Midazolam 5mg/ml, 5mg/5ml, 10mg/10ml

Depresses  Brain Rapidly **Maintains Sedation Continuously**

- Easier to perform procedures due to reduction of anxiety [1]
- Minimal effects on cardio-respiration & oxygen saturation[2]
- Significantly lower pain score & discomfort[3]

General Anesthesia Cascade

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION
↓
5. MAINTENANCE
↓
6. RECOVERY
↓
7. POST OPERATIVE MANAGEMENT

General Anesthesia Cascade

1 PREPARATION

Explain risk and benefits

MONITORING

ECG - ElectroCardioGraphy

SpO2 - Blood saturation with O2

BP monitoring

Oxygen measurement

Capnography- Measures amount of CO2 exhaled by patient

Temperature measurement

Electroencephalography if needed

General Anesthesia Cascade

1. **PREPARATION**

↓

2. **PREMEDICATION**

The initial psychological & pharmacologic component of anesthetics management is referred to as **“Premedication”**

It is administered orally or Intramuscularly 1 to 2 hours before the anticipated induction of anesthesia

Example: Opioids, Benzodiazepine, Antihistamines, Alpha-2 agonists, Anticholinergics (Glycopyrrolate) etc.

General Anesthesia Cascade

1. **PREPARATION**

↓

2. **PREMEDICATION**

↓

3. **ENDOTRACHEAL INTUBATION**

Intubation, is the placement of a flexible polyvinyl chloride tube into the trachea (windpipe) **to maintain an open airway or to serve as a conduit** through which to administer certain drugs.

Example: Atracurium, Vecuronium, Rocuronium and Cisatracurium.

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION

The administration of a drug or combination of drugs at the beginning of an anaesthetics that results in a state of general anaesthesia.

Example: Intravenous- Propofol etc;

Inhalational- Sevoflurane and Isoflurane

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION
↓
5. MAINTENANCE

Other commonly used drugs include:

Antihypertensives drugs (To treat high BP) eg: **Labetalol**

Ephedrine & phenylephrine (To treat low BP)

Salbutamol (To treat asthma or laryngospasm/bronchospasm)

Epinephrine or diphenhydramine (To treat allergic reactions)

To prolong unconsciousness for the required duration (usually the duration of surgery), anaesthesia must be maintained

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION
↓
5. MAINTENANCE
↓
6. RECOVERY

Example:

Anticholinergics-

Glycopyrrolate

Reversal agent-

Neostigmine

This time is critical because it is a period of physiologic disturbance during which crisis can arise.

Frequent observation and monitoring is required.

General Anesthesia Cascade

1. PREPARATION
↓
2. PREMEDICATION
↓
3. ENDOTRACHEAL INTUBATION
↓
4. INDUCTION
↓
5. MAINTENANCE
↓
6. RECOVERY
↓
7. POST OPERATIVE MANAGEMENT

Oral pain relief medications such as **paracetamol and NSAIDs (e.g., ibuprofen).**

Moderate levels of pain:

Tramadol

Anaesthesia should conclude with a pain-free awakening and a management plan for postoperative pain relief.

To provide skeletal muscle relaxation for endotracheal intubation & mechanical ventilation

℞

ATRAPURE

Inj. Atracurium Besylate 25mg/2.5 ml, 50mg/5ml, 100mg/10ml

FOR IV use only

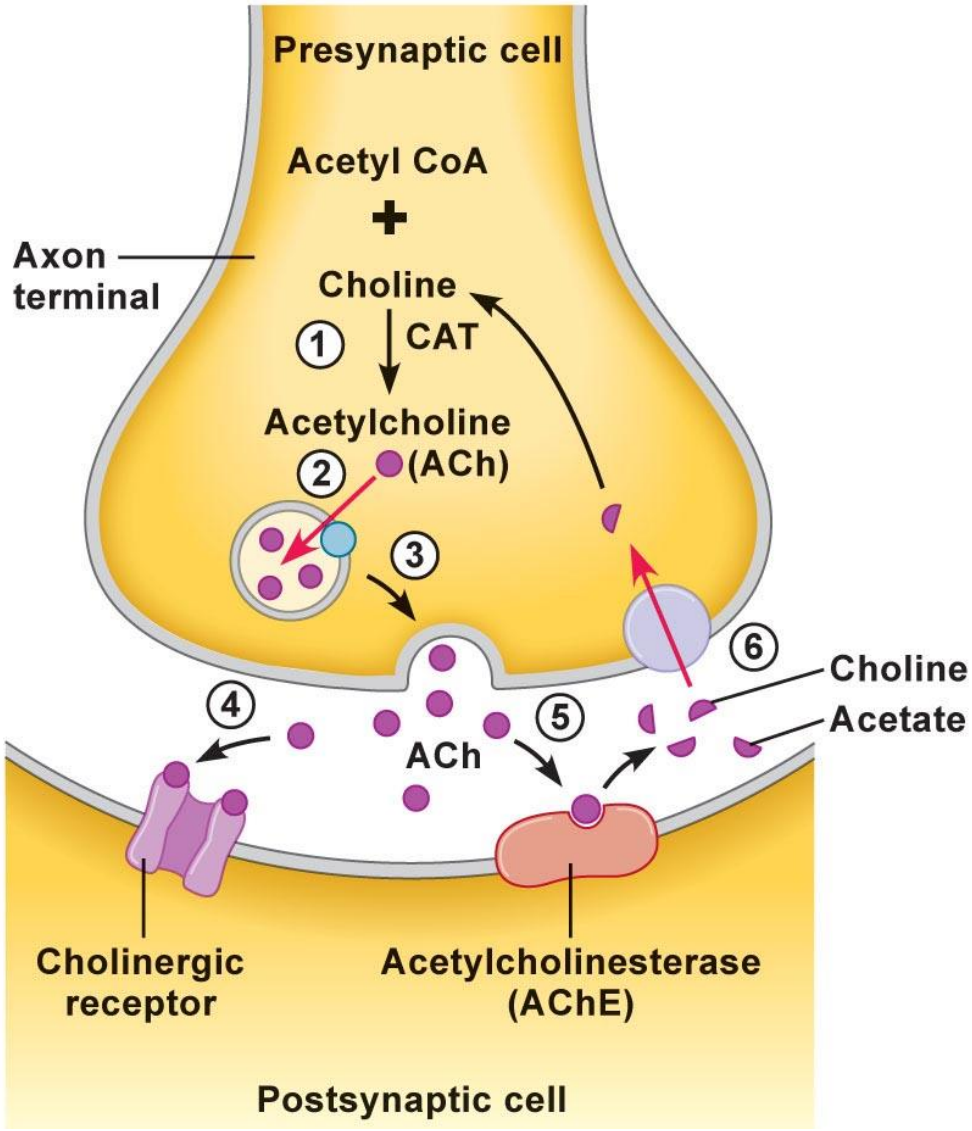
Product Introduction

DESCRIPTION:

- ATRAPURE (Atracurium Besylate) is an intermediate-duration, non depolarizing, skeletal muscle relaxant for intravenous administration.

Mechanism of action

- ATRAPURE is a non-depolarizing skeletal muscle relaxant.
- Non-depolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the muscle.


Presynaptic cell
Acetyl CoA
+
Axon terminal
Choline
1
CAT
Acetylcholine
2
(ACh)
3
6
Choline
Acetate
4
5
ACh
Cholinergic receptor
Acetylcholinesterase (AChE)
Postsynaptic cell

Pharmacokinetics

Bioavailability:	100% (IV)
Protein binding:	82%
Metabolism:	Hofmann elimination
Biological half-life:	17–21 minutes
Onset of action	2-3 min
Duration of action	20-35 min
Excretion	Renal 5%

https://reference.medscape.com/drug/atracurium-343103#10

Indication

- To facilitate endotracheal intubation
- Skeletal Muscle relaxation during surgery or mechanical ventilation

Target Customers

- Anaesthesiologist
- Intensivist

Dosage

Adults :

Initial Dose - 0.4 to 0.5 mg/ kg as IV bolus injection

Maintenance Dose - Required 20 to 45 minutes after initial dose.
Maintenance dose is 0.08 to 0.10 mg/kg

With Isoflurane or Enflurane dose - 0.25 to 0.35 min/kg

In ICU (Infusion) – 11 -13 mcg/kg/min.

Pediatric : > 2 years : No dose adjustments required
1 month to 2 years of age: 0.3 to 0.4 mg/kg as initial dose under halothane

- ATRAPURE should be administered Intravenously
- Do not give by ATRAPURE Intramuscular administration
- ATRAPURE is contraindicated in patients known to have a hypersensitivity

Dilution

- Infusion solutions of ATRAPURE (Atracurium Besylate) may be prepared by admixing ATRAPURE (Atracurium Besylate) Injection with an appropriate diluent such as 5% Dextrose Injection; 0.9% Sodium Chloride Injection;

- Spontaneous degradation of ATRAPURE (Atracurium Besylate) has been demonstrated to occur more rapidly in Lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection not be used as a diluent in preparing solutions of ATRAPURE (Atracurium Besylate) for infusion.

To provide skeletal muscle relaxation for endotracheal intubation & mechanical ventilation

Rx SAMVEC

Vecuronium Bromide for inj. 4mg, 10mg (Lyophilized)

Product Introduction

DESCRIPTION:

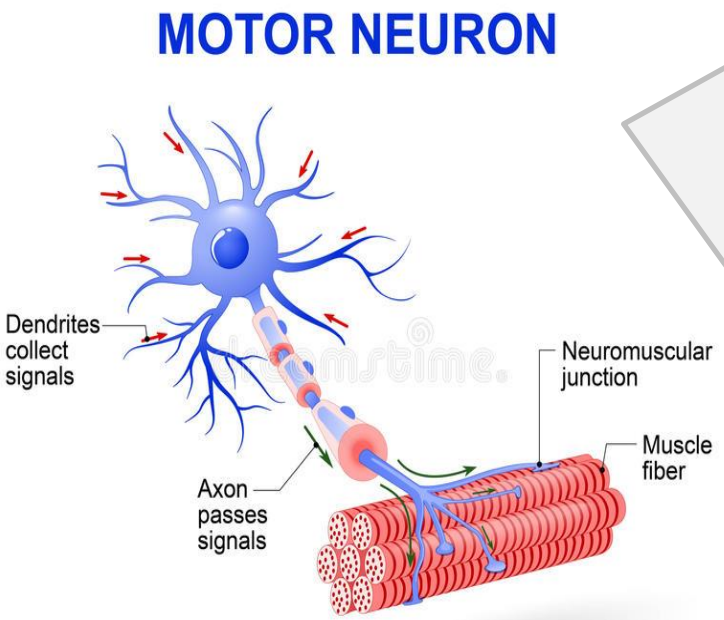
- SAMVEC (Vecuronium Bromide) is an Longer-duration acting, non depolarizing, skeletal muscle relaxant for intravenous administration.

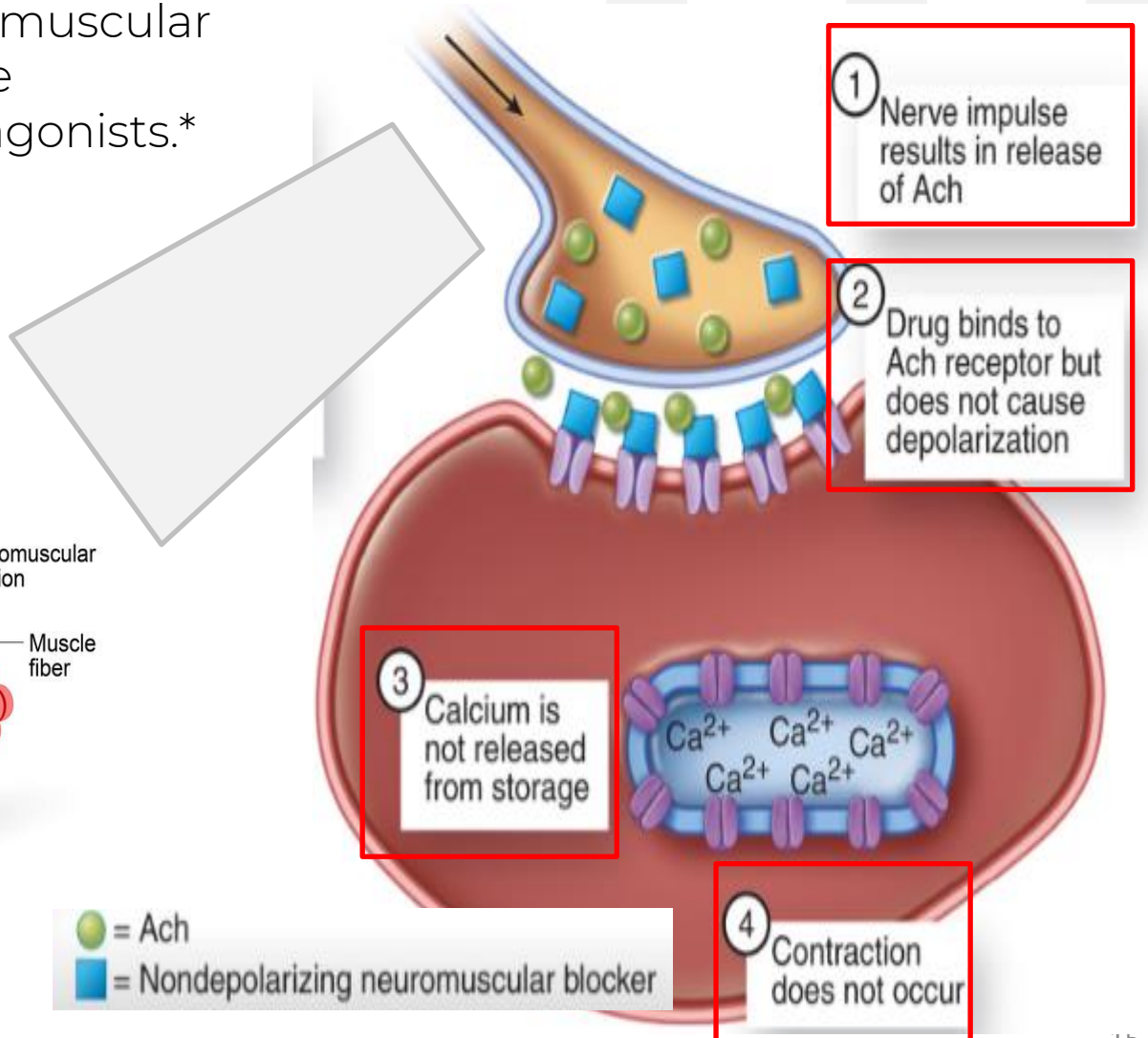
Mechanism of action

- SAMVEC is a non-depolarizing skeletal muscle relaxant.
- Non-depolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the muscle.

Vecuronium: Mechanism of Action

- Non-depolarizing neuromuscular blockers are competitive acetylcholine (ACh) antagonists.*





Reference: https://biology-forums.com/index.php?action=gallery;sa=view;id=28462. * Cook D, Simons DJ. Neuromuscular Blockade. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538301/

Pharmacokinetics

Bioavailability	100% (IV)
Metabolism	liver 30%
Onset of action	**3-5 minutes**
Biological half-life	31–80 minutes (longer with renal failure)
Duration of action	**20-35 mins**
Protein Bound:	60-90%
Excretion	Fecal (40-75%) and kidney (30% as unchanged drug and metabolites)

https://reference.medscape.com/drug/vecuronium-343110?pa=RlIt1zMee%2Fjmt6tO9x2mzifD%2BOvBWDQKWWKRZ2yCv3gUzd2u2%2B91wYEamvV5UEAGVrJxKJt4DRD8mxYr6kYfOw%3D%3D#10

Indication

- To facilitate endotracheal intubation
- Skeletal Muscle relaxation during surgery or mechanical ventilation

Target Customers

- Anaesthesiologist
- Intensivist

Dosage

Adults :

Reconstituted injection to the desired concentration (0.1 to 0.2 mg/ml)

Initial Dose - 80 to 100 mcg/kg by IV injection

Maintenance Dose - 10 to 15 mcg /kg as required during prolonged procedures

The usual doses may need to be reduced in the presence of certain drugs such as inhalation anesthetics which may potentiate competitive neuromuscular blockade

Pediatric : Same dose requirements (mg/kg)

- SAMVEC should be administered Intravenously
- Do not give by SAMVEC Intramuscular administration
- Dosage needs to be reduced if inhalation anesthetics are used.

Warnings

Warning

- Anaphylaxis
- Risk of Death due to Medication Errors

Special Population

Patient Population	Recommendations
Pregnancy	• It should be given only if clearly needed.
Nursing Mothers	• Caution should be exercised
Pediatric Use	• Less than 7 weeks of age have not been established
Geriatric Use	• Start with the low end of the dosing range and should be monitored
Renal Impairment	• A lower initial dose of vecuronium should be considered
Hepatic Impairment	• Not recommended as it is excreted by the liver

Contraindications

It is contraindicated in patients known to have a hypersensitivity to vecuronium.

Thank you

ATRACIS
(Cisatracurium)

ROCPURE
(Rocuronium)

Flow of Presentation

1. Lower Respiratory System

2. Tracheal Intubation

Tracheal Intubation Equipment
Range Of Clinical Indications For Tracheal Intubation
Indications Of Tracheal Intubation Under Emergency Conditions
Intubation Checklist

3. Medications Used During Intubation

4. Neuromuscular Blockade (NMB) & Agents

Where NMBAs Are Given?
What Do NMBAs Do?

5. History Behind The Use Of Non-depolarizing Muscle Relaxants

6. Cisatracurium Introduction

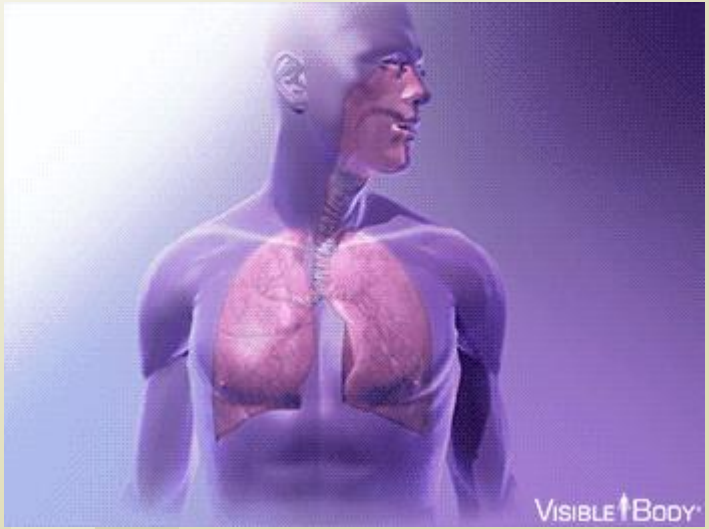
Cisatracurium: Product Profile, Mechanism Of Action, Dosage & Administration, Pharmacokinetics, Contraindications & Safety Profile, Use in Special Populations, Clinical Trials & Summary.

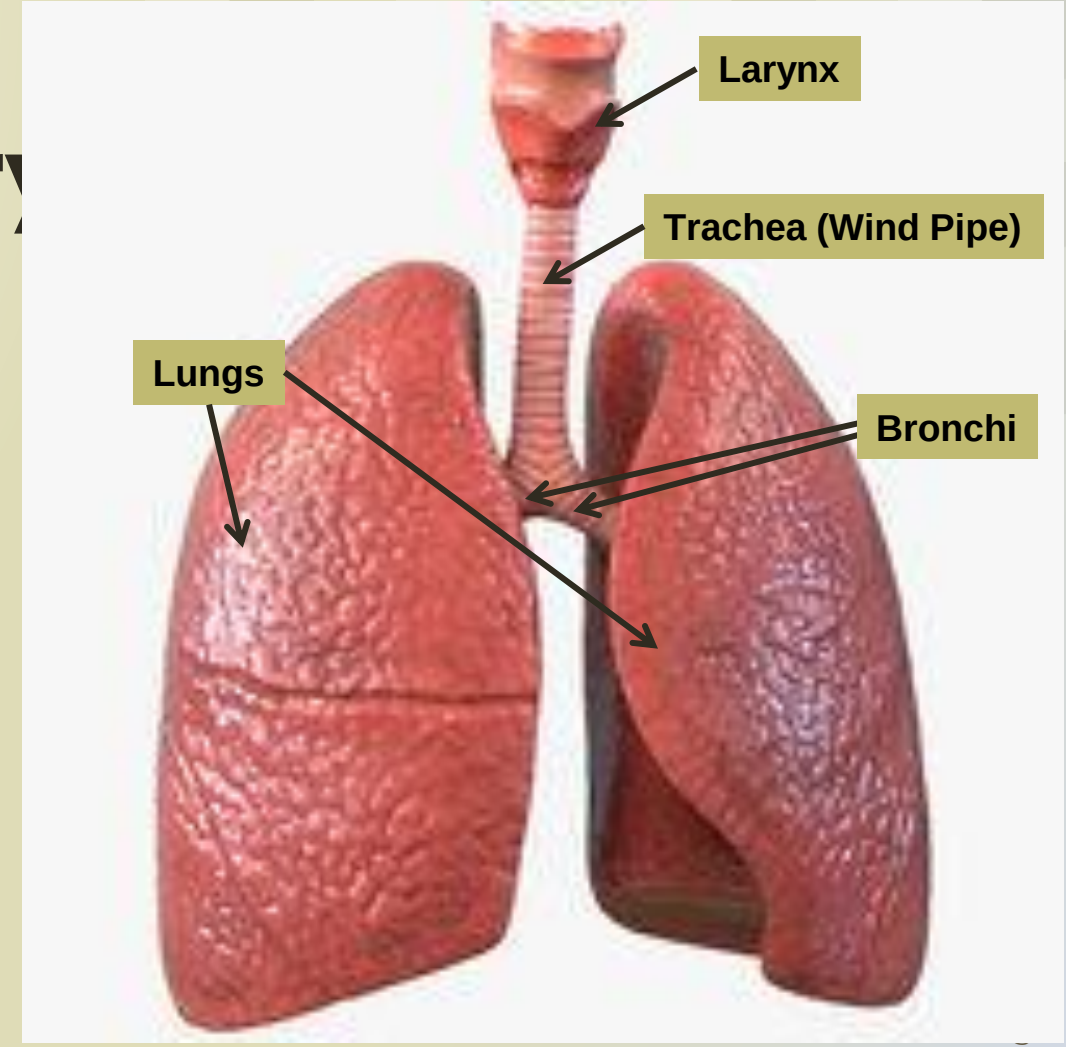
7. Rapid Sequence Intubation (RSI)

8. Rocuronium Introduction

Rocuronium: Product Profile, Mechanism Of Action, Dosage & Administration, Pharmacokinetics, Contraindications & Safety Profile, Use in Special Populations, Clinical Trials & Summary.

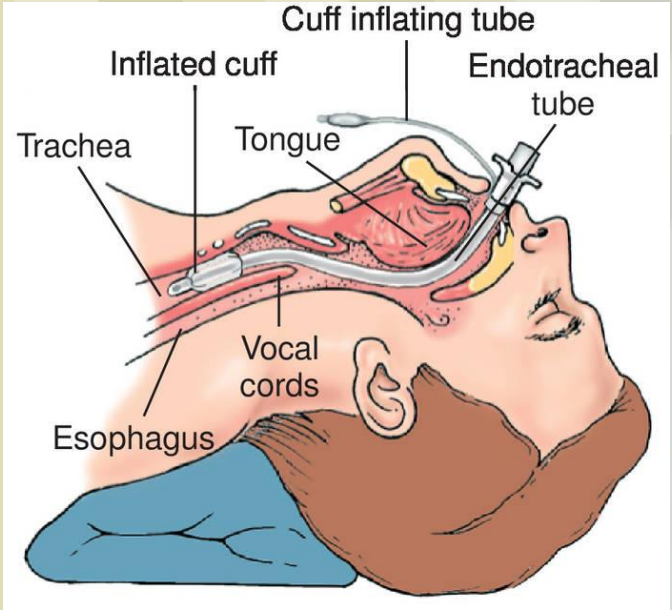
Lower Respiratory System





Tracheal Intubation

Endotracheal intubation is the process by which a tube is inserted into the trachea. This can be done through the larynx.[1]



Tracheal intubation allows-[2]

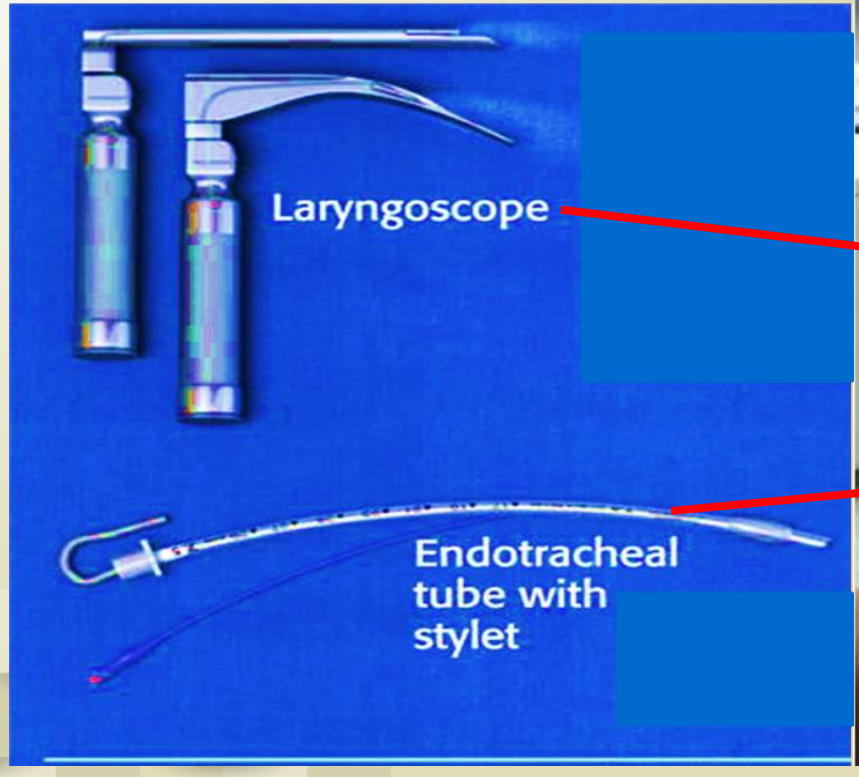
- Tracheobronchial suction (removing secretions)
- Lung expansion
- Oxygenation and ventilation until adequate reversal of muscle relaxation and return to spontaneous breathing.

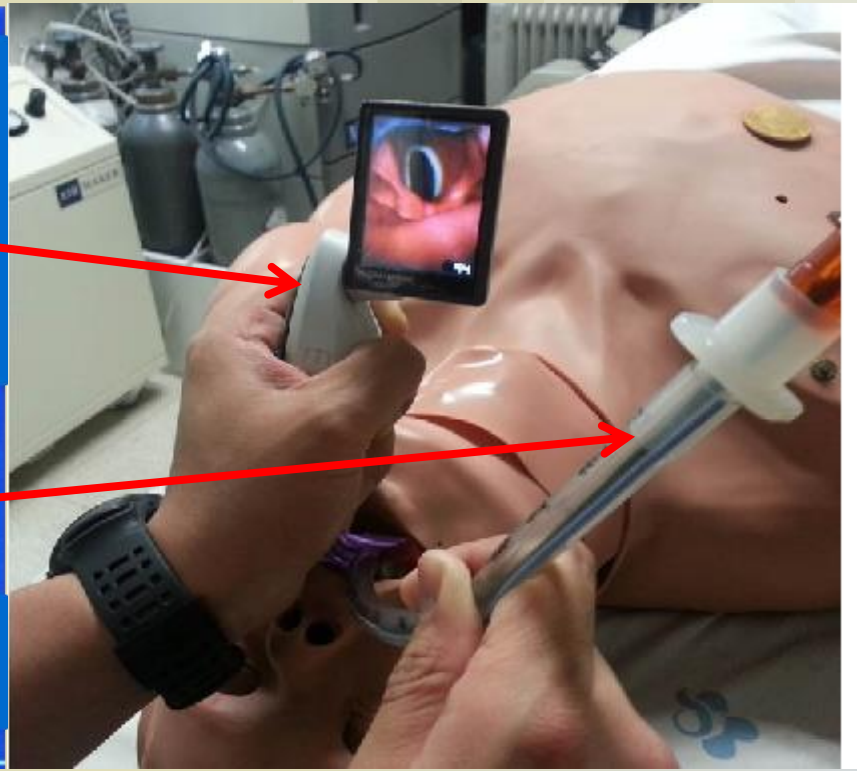
Application of this Method-[3]

In the setting of respiratory failure and shock.

Reference: 1. Shepard B. Stone, in Essential Clinical Procedures (Second Edition), 2007; 2. Ira S. Landsman, et al. Chapter 24 - Anesthesia for Pediatric Otorhinolaryngologic Surgery. Smith's Anesthesia for Infants and Children (8th Edition),2011;786-820.; 3. 1. Divatia JV, Khan PU, Myatra SN. Tracheal intubation in the ICU: Life saving or life threatening? Indian J Anaesth. 2011 Sep;55(5):470-5

Tracheal Intubation Equipment





Reference: Br J Anaesth. 2018 Feb;120(2):323-352.

Range Of Clinical Indications For Tracheal Intubation

Airway problems: tumor or infection.	**Respiratory deficiencies:** patients with hypoxemic, respiratory insufficiency condition.	**Muscle and central nervous system problems and metabolic disorders:** diseases of the muscles of respiratory system.	**For the purpose of examination and transfer of patients:** If respiratory issue MRI scan, endoscopic procedures.	**If urgent aggressive sedation is required to protect the patient**	**In head and neck surgery**

Reference: Şahiner Y. Indications for endotracheal intubation. InTracheal Intubation 2018 Jul 25. IntechOpen.

Indications Of Tracheal Intubation Under Emergency Conditions

Apnea (shortness of breathe-Asthma), **respiratory failure.**	**Airway obstruction:** variable-level obstruction in the upper and lower airways.	**In case the patient is hemodynamically unstable.**	**In case the treatment of patient is not successful without intubation.**

Reference: Şahiner Y. Indications for endotracheal intubation. InTracheal Intubation 2018 Jul 25. IntechOpen.

Intubation Checklist

Prepare the team

- ❑ **Allocate roles**

One person may have more than one role.

- ❑ Team Leader
- ❑ 1st Intubator
- ❑ 2nd Intubator
- ❑ Cricoid force
- ❑ Intubator's assistant
- ❑ Drugs
- ❑ Monitoring patient
- ❑ Runner
- ❑ MILS (if indicated)
- ❑ Who will perform FONA?

- ❑ **Who do we call for help?**
- ❑ **Who is noting the time?**

Prepare the equipment

- ❑ **Apply monitors**
  - ❑ SpO_2 / waveform $ETCO_2$ / ECG / BP
- ❑ **Check equipment**
  - ❑ Tracheal tubes x 2 - cuffs checked
  - ❑ Direct laryngoscopes x 2
  - ❑ Videolaryngoscope
  - ❑ Bougie / stylet
  - ❑ Working suction
  - ❑ Supraglottic airways
  - ❑ Guedel / nasal airways
  - ❑ Flexible scope / Aintree
  - ❑ FONA set
- ❑ **Check drugs**
  - ❑ Consider ketamine
  - ❑ Relaxant
  - ❑ Pressor / inotrope
  - ❑ Maintenance sedation

Prepare the patient

- ❑ **Reliable IV / IO access**
- ❑ **Optimise position**
  - ❑ Sit-up?
  - ❑ Mattress hard
- ❑ **Airway assessment**
  - ❑ Identify cricothyroid membrane
  - ❑ Awake intubation option?
- ❑ **Optimal preoxygenation**
  - ❑ 3 mins or ETO_2 > 85%
  - ❑ Consider CPAP / NIV
  - ❑ Nasal O_2
- ❑ **Optimise patient state**
  - ❑ Fluid / pressor/ inotrope
  - ❑ Aspirate NG tube
  - ❑ Delayed sequence induction
- ❑ **Allergies?**
  - ❑ ↑ Potassium risk?

Prepare for difficulty

- ❑ **Can we wake the patient if intubation fails?**
- ❑ **Verbalise** "Airway Plan is:"
  - ❑ **Plan A:** Drugs & laryngoscopy
  - ❑ **Plan B/C:** Supraglottic airway Face-mask Fibreoptic intubation via supraglottic airway
  - ❑ **Plan D:** FONA Scalpel-bougie-tube
- ❑ **Does anyone have questions or concerns?**

Abbreviation:
IV: intravenous. IO: intra-osseous. ETO2: end-tidal oxygen. CPAP: continuous positive airway pressure. NIV: non-invasive ventilation. NG: naso-gastric.

Reference: British Journal of Anaesthesia.2018;120 (2): 323e352.

Medications Used During Intubation

The classes of medications commonly used include the following:

- Parasympathetic blocker
- Sedation and analgesia
- Neuromuscular blocking agents (NMBA)

Reference: Advanced Emergency Nursing Journal. 2018;40(3):183–193.

Neuromuscular Blockade (NMB) & Agents

Neuromuscular blockade is frequently used in:

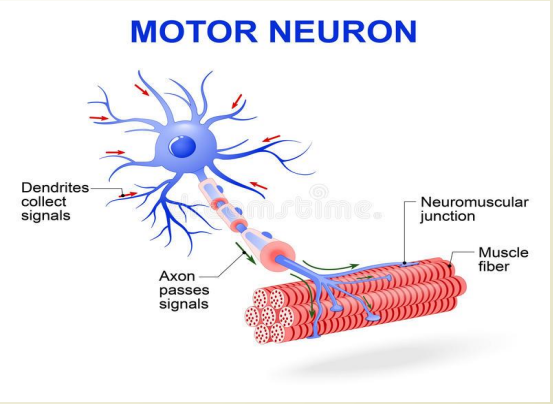
- Anesthesia to facilitate endotracheal intubation
- Optimize surgical conditions
- Assist with mechanical ventilation in patients who have reduced lung compliance.

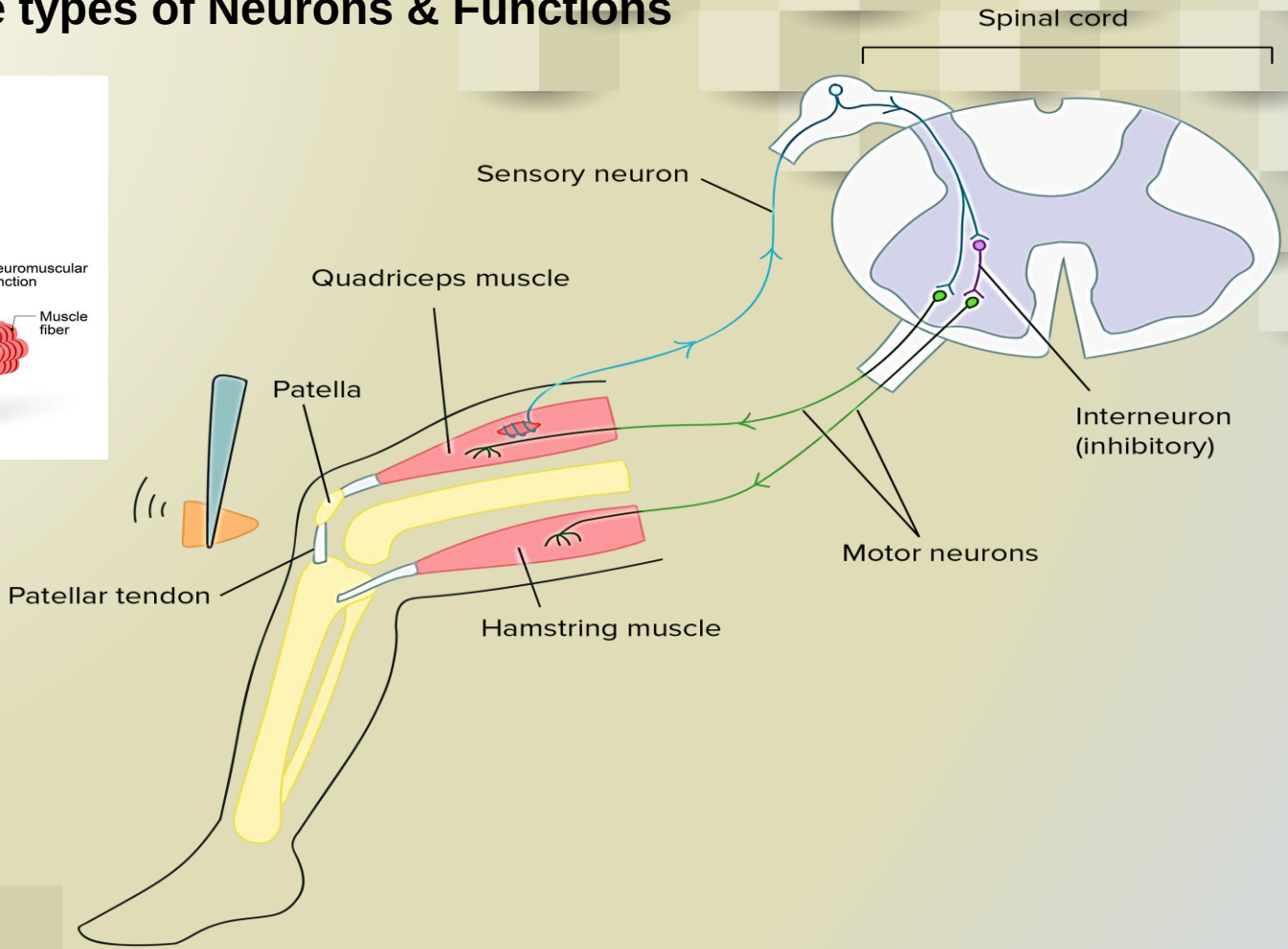
Neuromuscular blocking agents (NMBAs) are two forms:

- Depolarizing neuromuscular blocking agents
- Non-depolarizing neuromuscular blocking agents

Reference: Cook D, Simons DJ. Neuromuscular Blockade. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538301/

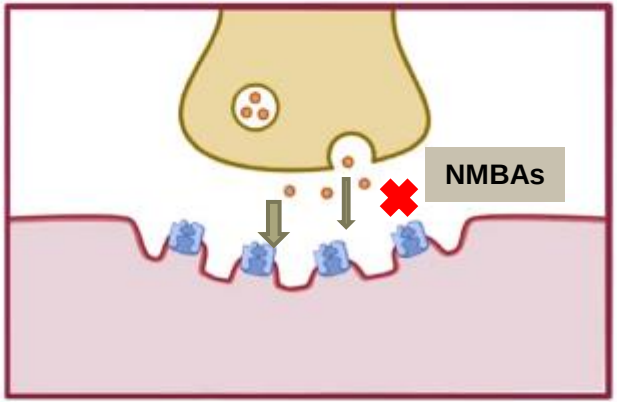
Understanding the types of Neurons & Functions

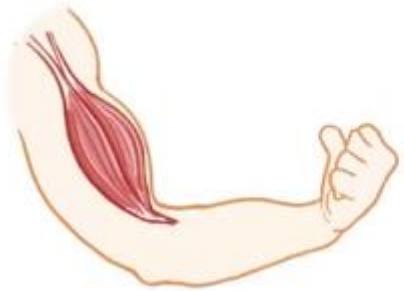




What Do NMBAs Do?

PREVENT ACETYLCHOLINE at NEUROMUSCULAR JUNCTION

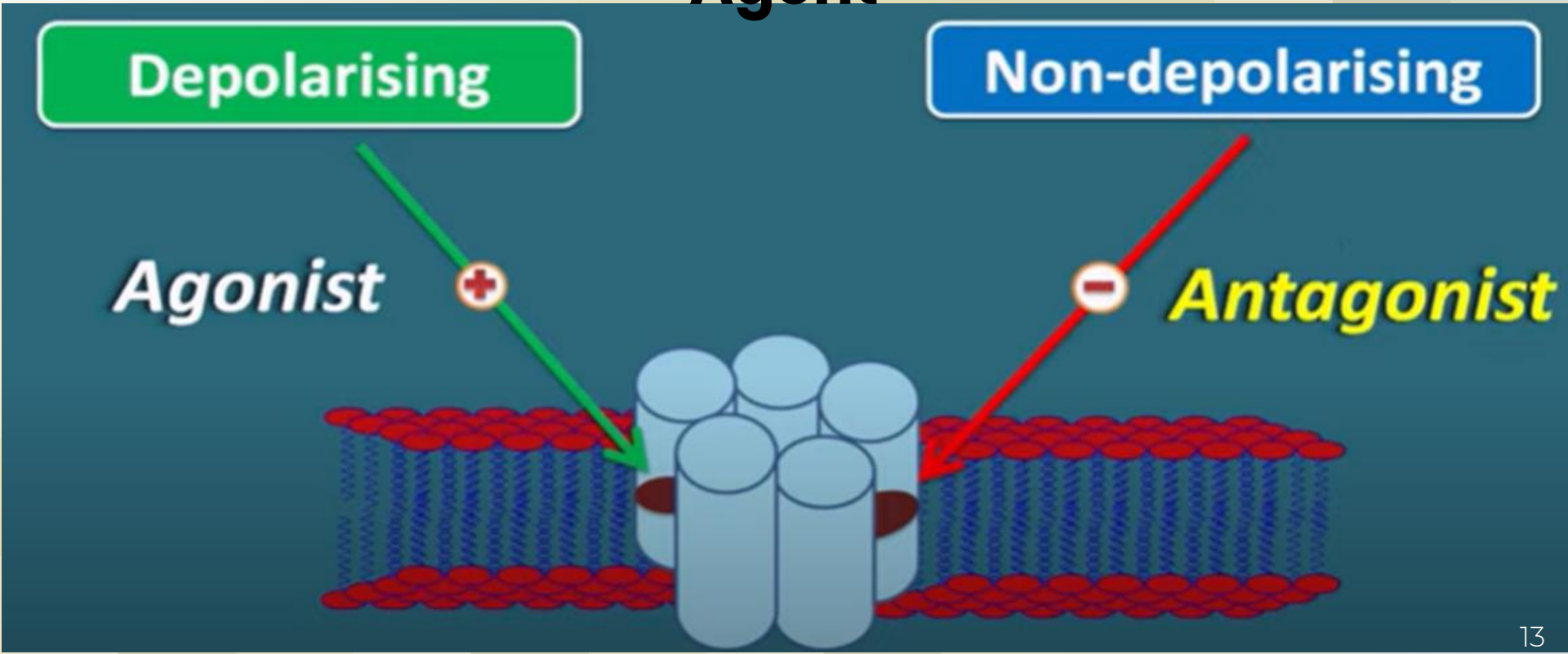




PREVENTS TRIGGERING of SKELETAL MUSCLE CONTRACTIONS

Reference: https://www.osmosis.org/learn/Neuromuscular_blockers

Difference in Depolarizing & Non-depolarizing Agent



History Behind The Use Of Non-depolarizing Muscle Relaxants

- Succinylcholine was used routinely to aid intubation due to its rapid onset of action and reliable neuromuscular blockade, leading to profound relaxation of the cords.

Problem with succinylcholine use: Side effect profile

Muscle pain, hyperkalemia, and pressure changes in the ocular and intracranial compartments.

All this led to the use of non-depolarizing muscle relaxants.

The non-depolarizing muscle relaxants which are currently in use in clinical practice are vecuronium, atracurium, cisatracurium and rocuronium.

Reference: Ramaiah, et al.: Comparison of Intubating Conditions between Cisatracurium and Rocuronium. International Journal of Scientific Study. 2020;8(5).

ATRACURIUM

- **Associated with histamine release at higher doses.[1]**
- Atracurium has been associated with **persistent neuromuscular weakness.[1]**
- Atracurium causes dose-dependent **histamine release (which is more common in adults than in children)[3], resulting in tachycardia and hypotension**[4]

histamine release- itching, contrists muscle in the lungs and makes harder to breathe

Reference: 1. Michael J. Murray, ... William T. Browne, in Critical Care Medicine (Third Edition), 2008.; 2. Journal of Anesthesiology. September 2019; 11(3): 257-261.; 3. Peter J. Davis, ... Susan Woelfel, in Smith's Anesthesia for Infants and Children (Eighth Edition), 2011.; 4.. Mona U. Shah, in Side Effects of Drugs Annual, 2016 4.. Charles J. Coté, ... Nishan Goudsouzian, in A Practice of Anesthesia for Infants and Children (Fourth Edition), 2009.

INTRODUCING

Cisatracurium: Introduction

- Cisatracurium besilate (cisatracurium), is approximately 5 times more potent than atracurium and about five times less laudanosine (a metabolite that crosses BBB and cause convulsions) is produced and lesser side effects.[1]
- Recovery properties of cisatracurium are affected by neither the size of the bolus dose nor by the duration of infusion.[2]
- Does not trigger histamine release.[2]
- Cisatracurium undergoes Hofmann elimination[2] (a mechanism that is independent of renal or hepatic function, other neuromuscular blockade agents may have continued effect after the infusion has been stopped, potentially increasing the need for sedation and mechanical ventilation)[3].

Reference: 1. Rochana G Bakhshi et al. JMSCR. 2016;4(12):14613-14621.; 2. Sparr, H.J., et al. Newer Neuromuscular Blocking Agents. Drugs.2001;61:919–942.; 3.Sottile PD et al. Am J Respir Crit Care Med. 2018;197(7):897–904

Cisatracurium: Product Profile

Approval in India: March 2016

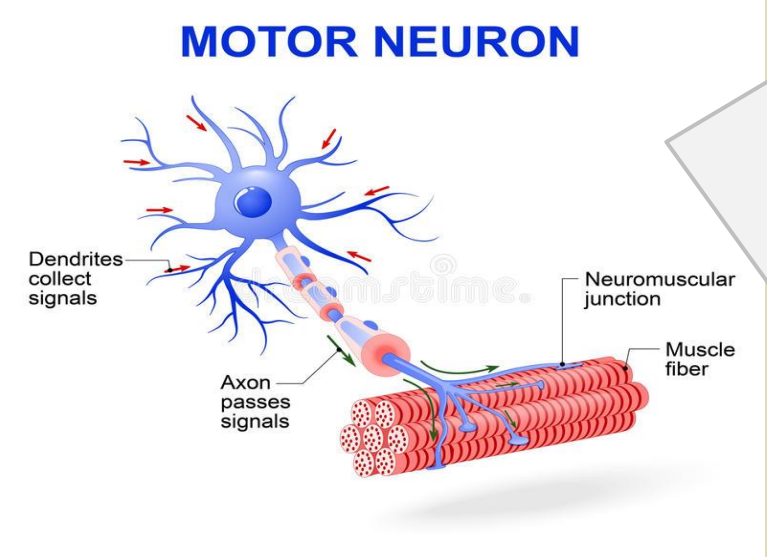
Strength: Cisatracurium 10mg/5ml and 20mg/10ml

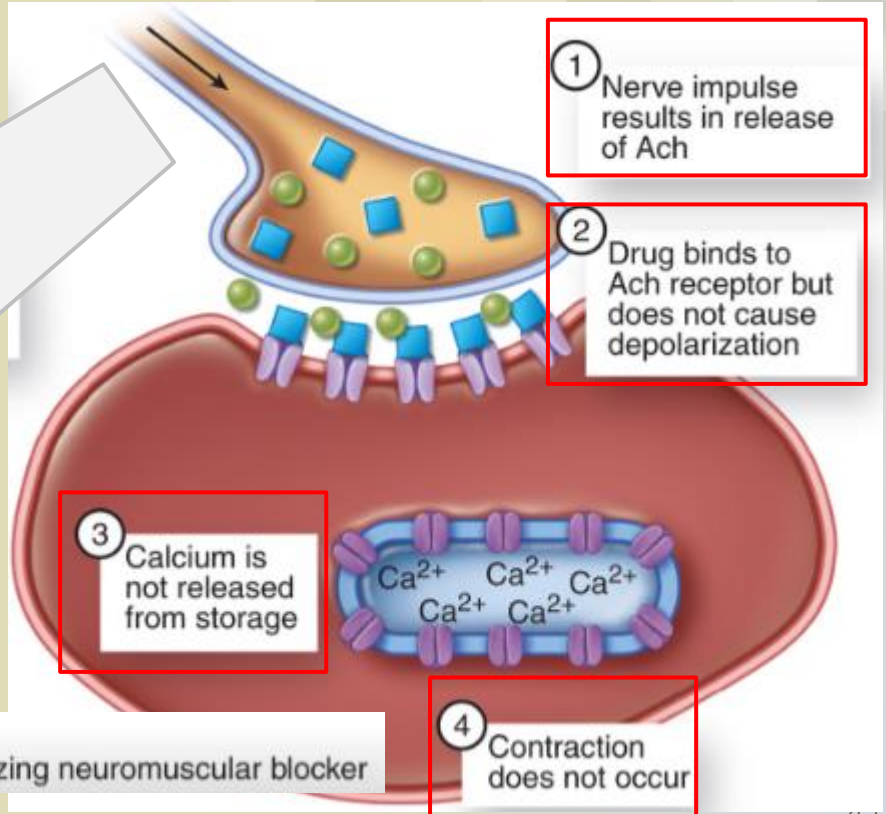
Approved Indications: As an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery.

Reference: As accessed on 27th July 2021 - https://cdscoonline.gov.in/CDSCO/Drugs

Cisatracurium: Mechanism of Action

- Non-depolarizing neuromuscular blockers are competitive acetylcholine (ACh) antagonists.*





Reference: https://biology-forums.com/index.php?action=gallery;sa=view;id=28462. * Cook D, Simons DJ. Neuromuscular Blockade. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538301/

Cisatracurium: Dosage & Administration

Tracheal Intubation in Adults

Starting dose 0.15 mg/kg and 0.2 mg/kg administered by bolus intravenous injection.

Doses up to 0.4 mg/kg have been safely administered by bolus intravenous injection to healthy patients and patients with serious cardiovascular disease.

Maintenance Bolus Cisatracurium Doses in Adult Surgical Procedures

Maintenance bolus dose of cisatracurium is 0.03 mg/kg; however, smaller or larger maintenance doses may be administered based on the required duration of action.

Administer the first maintenance bolus dose starting:

- 40 to 50 minutes after an initial dose of 0.15 mg/kg;
- 50 to 60 minutes after an initial dose of 0.2 mg/kg

Reference: International PI US, July 2018.

Cisatracurium: Dosage & Administration

Tracheal Intubation in Pediatric Patients

Infants 1 to 23 Months of Age

For intubation is **0.15 mg/kg administered over 5 to 10 seconds.**

Pediatric Patients 2 to 12 Years of Age

Bolus dose of 0.1 to 0.15 mg/kg administered over 5 to 10 seconds.

Reference: International PI US, July 2018.

Cisatracurium: Pharmacokinetics

Elimination half life: 22-29 mins

Plasma protein binding: The binding of cisatracurium to plasma proteins **has not been successfully studied** due to its rapid degradation at physiologic pH.

Elimination: Organ-independent Hofmann elimination is the predominant pathway for the elimination of cisatracurium.

Reference: International PI US, July 2018.

Cisatracurium: Contraindications

Known hypersensitivity to cisatracurium.

Severe hypersensitivity reactions, have been reported. Precautions should also be taken in those patients who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents, both depolarizing and non-depolarizing, has been reported.

Reference: 1. International PI US, July 2018.

Cisatracurium: Safety Profile

The **most common adverse reactions (0.1% to 0.4%)** were bradycardia, hypotension, flushing, bronchospasm, and rash.

Reference: International PI US, July 2018.

Cisatracurium: Use in Special Populations

❖ Pregnancy

There are no adequate and well-controlled studies of Cisatracurium in pregnant women.[1] Cisatracurium should not be used during pregnancy.[2]

❖ Lactation

It is not known whether cisatracurium besylate is present in human milk.[1]

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cisatracurium and any potential adverse effects on the breastfed child from cisatracurium or from the underlying maternal condition.[1]

Reference: 1. International PI US, July 2018. 2. International PI UK, July 2021.

Cisatracurium: Use in Special Populations

❖ Pediatric Use

The safety and effectiveness of Cisatracurium have not been established in pediatric patients less than 1 month of age.

❖ Geriatric Use

The time to maximum neuromuscular blockade is approximately 1 minute slower in geriatric patients compared to younger patients, **consider extending the interval between administering cisatracurium and attempting intubation by at least 1 minute to achieve adequate intubation conditions.**

Reference: International PI US, July 2018.

Cisatracurium: Use in Special Populations

❖ **Patients with Hepatic Impairment**

The times to maximum neuromuscular blockade were approximately 1 minute faster in liver transplant patients than in healthy adult patients receiving 0.1 mg/kg cisatracurium.

❖ **Patients with Renal Impairment**

Consider extending the interval between administering cisatracurium and attempting intubation by at least 1 minute to achieve adequate intubation conditions.

Reference: International PI US, July 2018.

Cisatracurium Vs. Atracurium Clinical Trials

Indications

Rapid Onset of Action

Longer Duration of Action

Optimal intubation

Better Hemodynamic Profile

Safety Profile

CLINICAL TRIAL I

INDIAN TRIAL

In Adults Surgical

crossref DOI: https://dx.doi.org/10.18535/jmscr/v4i12.52

IGM Publication

Journal Of Medical Science And Clinical Research

An Official Publication Of IGM Publication

Comparison of Neuromuscular Blockade and Recovery Characterstics of Cisatracurium Besylate versus Atracurium Besylate in Adult Surgical Patients

Authors

Dr Rochana G Bakhshi[1], Dr Anisha Nagaria[2], Dr Shubha N Mohite[3], Dr Gurlyn Ahluwalia[4]

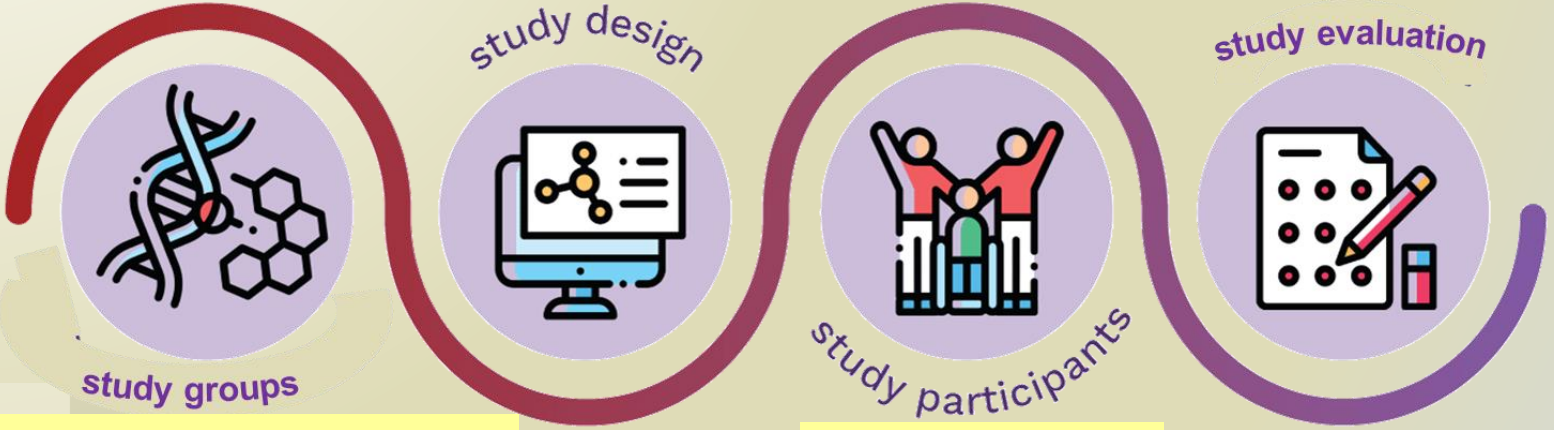
The study aimed to compare neuromuscular blockade and recovery characteristics of cisatracurium and atracurium in adult patients.

Reference: Dr Rochana G Bakhshi et al. JMSCR.2016 ;4(12).

Study Methodology…

Prospective, double-blind, randomized trial

The onset time was determined as the interval from the end of muscle relaxant injection until “Train of four (TOF) score 0”.



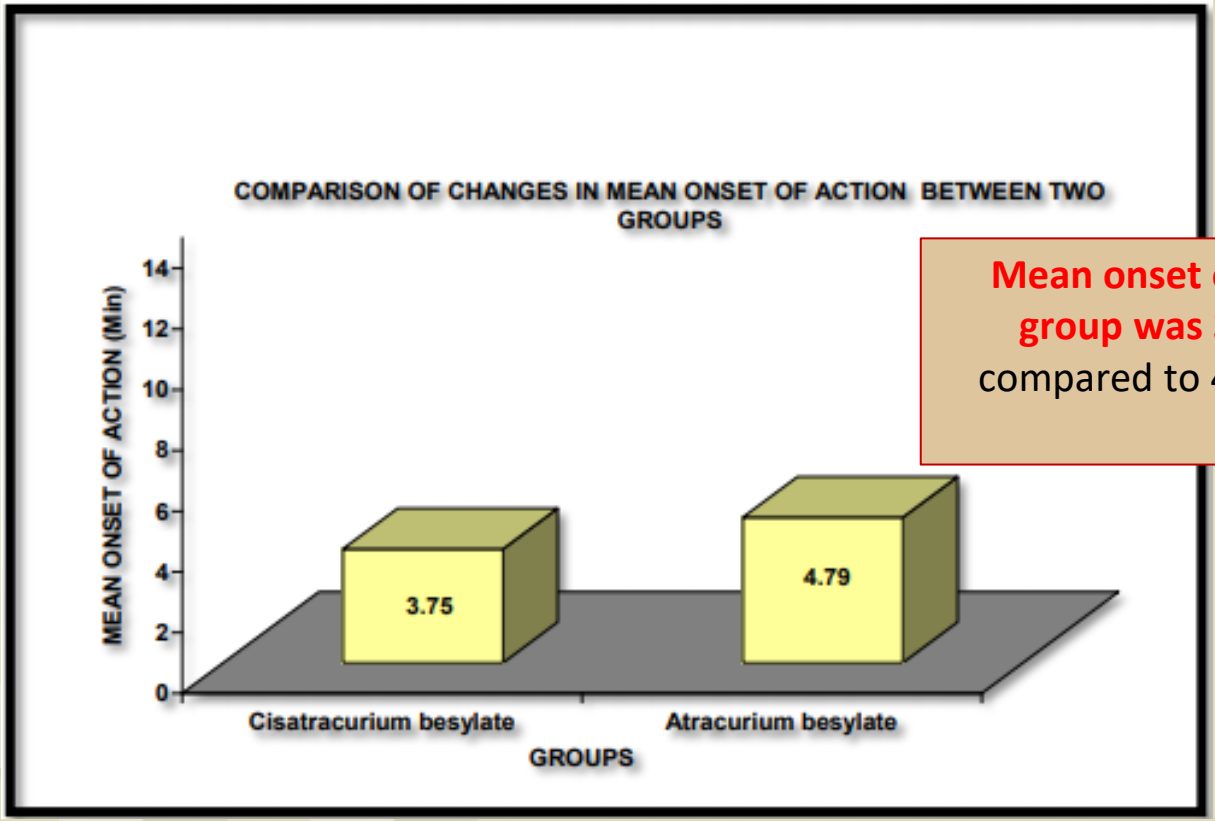
Group A: Atracurium with initial dose of 0.5 mg/kg , maintenance dose of 0.1mg/kg
Group B: Cisatracurium with initial dose of 0.2 mg/kg maintenance dose of 0.03mg/kg

N= 60 (18-65 yrs) patients

Reference: Dr Rochana G Bakhshi et al. JMSCR.2016 ;4(12).

Study Results…

Comparison of changes in mean onset of action



Mean onset of action in Cisatracurium besylate group was 3.75 minutes which was faster as compared to 4.79 minutes in Atracurium besylate group.

Reference: Dr Rochana G Bakhshi et al. JMSCR.2016 ;4(12).

Study Conclusion…

Cisatracurium in a dose of 0.2mg/kg had a faster onset and duration of action as compared to atracurium(0.5mg/kg).

Cisatracurium recovery was faster and without any residual muscle paralysis.

There were no adverse drug reactions observed in cisatracurium group.

Cisatracurium even with the higher dose is safe and more efficacious

Reference: Dr Rochana G Bakhshi et al. JMSCR.2016 ;4(12).

CLINICAL TRIAL II

INDIAN TRIAL

Abdominal Surgeries

Original Article

Cisatracurium versus Atracurium for Abdominal Surgeries Regarding Condition of Intubation and Hemodynamic Effect: A Randomized Double-Blind Study

Rahul Ranjan, Mohammad Faseehullah Alam, Raja Avinash

Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar India

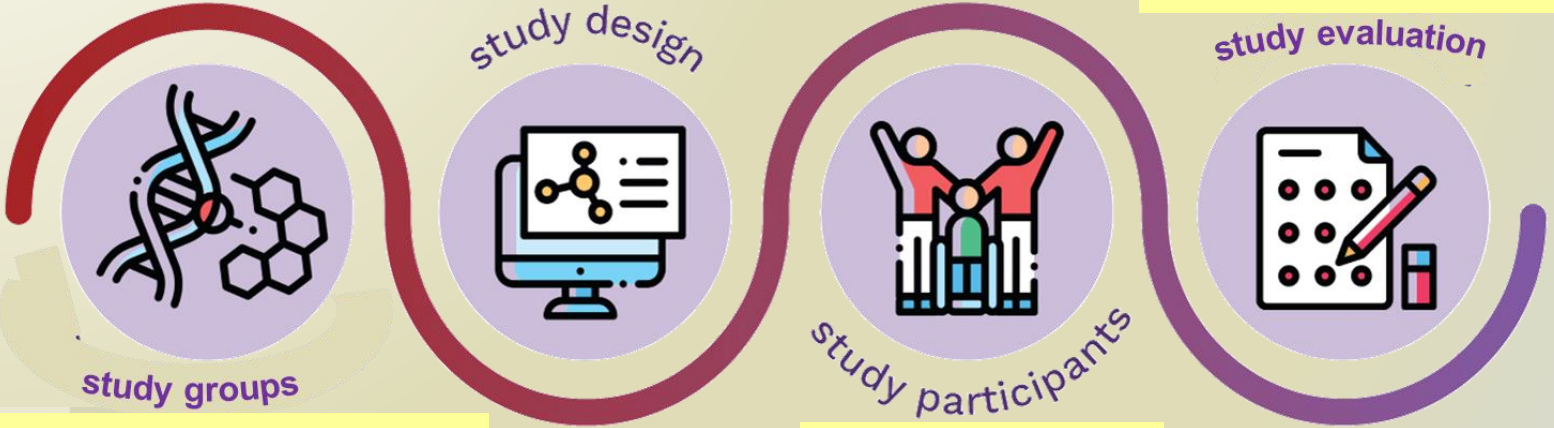
This study was conducted to compare the atracurium and cisatracurium concerning neuromuscular blockade and recovery characteristics.

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Methodology…

Prospective randomized study

Efficacy of both the drugs was compared in terms of onset of action, duration of action, duration of recovery, hemodynamic conditions during and after intubation, and signs of histamine release in both the drugs.



100 patients divided into two groups of 50 each. Group A received atracurium (0.5 mg/kg), whereas **Group B** received cisatracurium (0.15 mg/kg).

N= 100 patients

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Results…

Comparison of atracurium and cisatracurium in terms of onset time

Onset time (s)	Frequency (%)		*P**
	Group A	Group B	
160-180	10 (20)	14 (28)	0.075
181-200	29 (58)	30 (60)	
>200	11 (22)	6 (12)	
Total	50 (100)	50 (100)	
Mean±SD	188.30±11.59	183.20±18.00	

*Unpaired *t*-test. SD: Standard deviation

Cisatracurium had faster onset of action 183.20 ± 18.00 s compared to atracurium 188.30 ± 11.59.

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Results…

Duration of action

Variables	Group A	Group B	*P*
Duration of action (min)	44.90±2.45	70.14±1.87	<0.001*
Duration of 25% recovery (min)	32.40±1.90	49.46±1.86	<0.001**
Time of recovery from reversal (min)	1.80±0.75	2.18±0.82	0.02**

*Unpaired *t*-test, **Chi-square test

The mean **duration of action in the cisatracurium group was 70.14 ± 1.87 min which was more and statistically significant (P = 0.001)** compared to 44.9 ± 2.45 min in the atracurium group.

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Results…

Adverse reaction comparison

Adverse effects	Group A	Group B	*P**
Flush	1	0	1.00
Erythema	1	0	
Wheal	0	0	

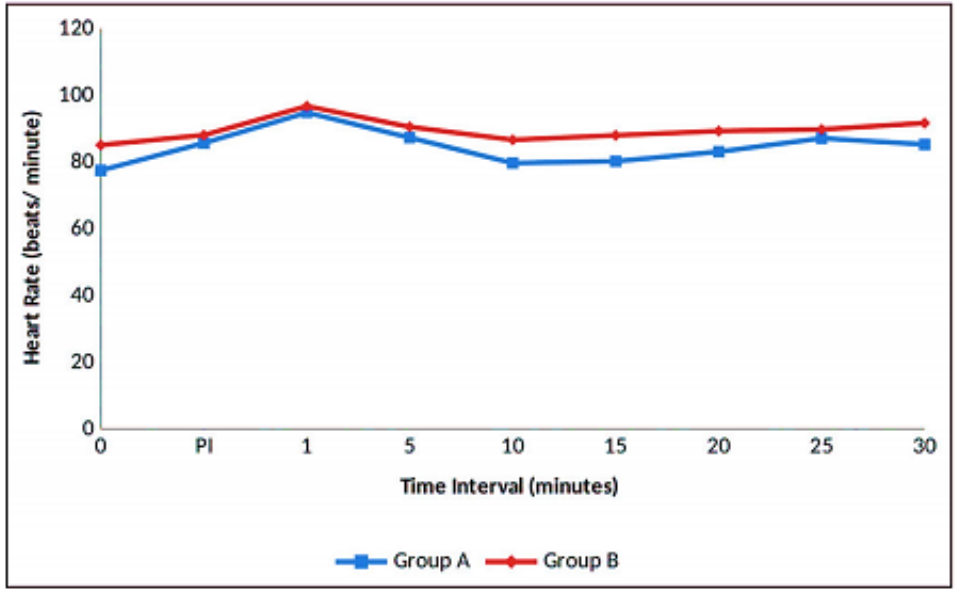
*Chi-square test

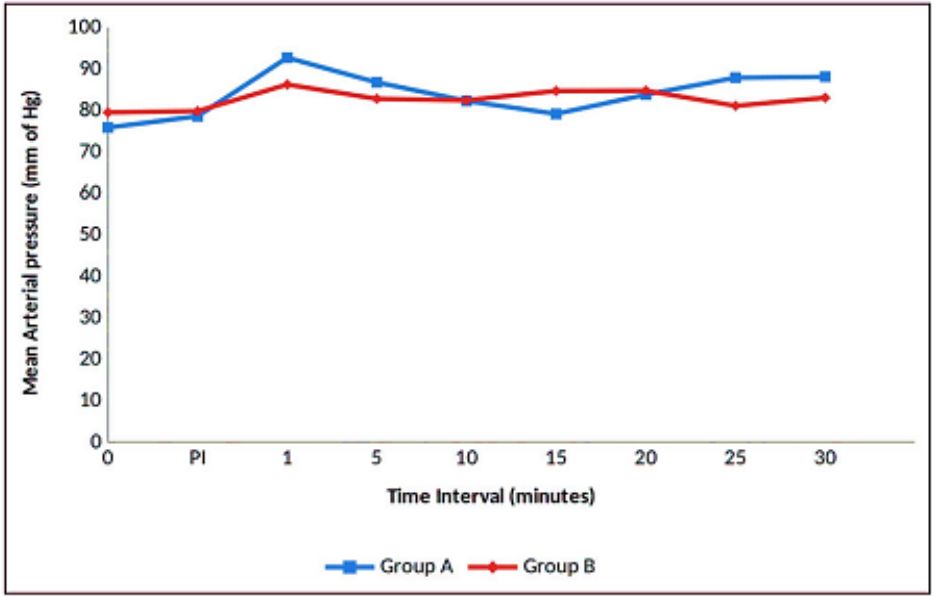
No signs of histamine release were noted in Group B, as compared to two cases in Group A.

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Results…

Comparison of Mean heart rate Mean arterial blood pressure in both groups





Cisatracurium is associated with more stable hemodynamics than atracurium.

Reference: Bali J Anaesthesiol 2021;5:93-7.

The Study Also Evaluated CCS

Copenhagen Consensus Conference **(CCS)** score.[14] Laryngoscopy, vocal cord position and movement, and response to intubation are each assigned a grade of excellent, good or poor. Any score of poor produces an overall score of 'clinically unacceptable', otherwise conditions are defined as 'clinically acceptable'. Acceptable conditions may be subdivided into 'excellent' and 'good'

Reference: International Journal of Scientific Study. 2020;8(5).

Study Results…

Intubating condition of cisatracurium & atracurium according to Copenhagen consensus scoring system

Parameters, *n* (%)	Group A	Group B	*P*
Laryngoscopy			
Easy	37 (74)	40 (80)	-
Fair	11 (22)	10 (20)	
Impossible	2 (4)	0 (0)	
Vocal cords			
Opened	36	41	-
Moving	12	9	
Closed	2	0	
Cough			
None	38	42	-
≤2	9	6	
>2	2	2	
Jaw relaxation			
Relaxed	35	38	-
Increased tone	11	10	
Rigid	4	2	
Limb movement			
None	33	37	-
Slight	11	8	
Severe	6	5	
CCS (mean±SD)			
Excellent	35.80±1.92	39.5±1.87	<0.0001*
Good	10.80±1.09	8.70±1.50	<0.0001*
Poor	3.2±1.79	1.83±1.83	<0.0003*

*Analyses done by unpaired *t*-test. CCS: Copenhagen consensus scoring, SD: Standard deviation

The studied dose, **Cisatracurium (0.15 mg/kg) gave optimal intubating conditions** compared to atracurium.

Reference: Bali J Anaesthesiol 2021;5:93-7.

Study Conclusion…

Cisatracurium in a dose of 0.15 mg/kg had a faster onset of action than atracurium 0.5 mg/kg. At this dose, **cisatracurium provides optimal intubating condition, rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, no signs of histamine release clinically, and without any residual muscle paralysis** compared to atracurium.

Reference: Bali J Anaesthesiol 2021;5:93-7.

CLINICAL TRIAL III

INDIAN TRIAL

In Hemodynamically Unstable Patients

IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver.10 March. (2018), PP 51-52
www.iosrjournals.org

Safety Comparison of Cisatracurium And Atracurium In Patients Undergoing General Anaesthesia

Manisha Bhagat[1], Ekramul Haque[2],Avinash Mishra[3]
R.I.M.S., Ranchi, Jharkhand, India
Corresponding Author: Manisha bhagat

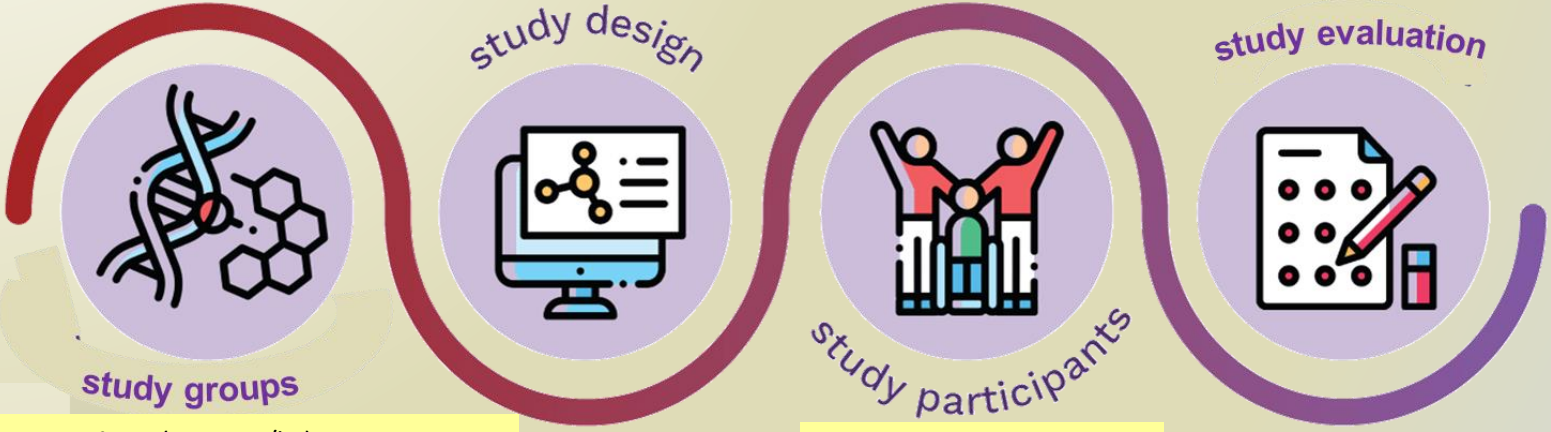
The study aimed evaluate the safety profile and differences between cisatracurium and atracurium, widely used in adult patients for general anesthesia.

Reference: IOSR Journal of Dental and Medical Sciences; 17(3); PP 51-52.

Study Methodology…

Prospective, randomized trial

For each patient the ADR monitoring was performed and ADR form was completed.



Cisatracurium: (0.15 mg/kg)
Atracurium: (0.6 mg/kg).

N= 80 patients

Reference: IOSR Journal of Dental and Medical Sciences; 17(3); PP 51-52.

Study Results…

Comparison of Adverse Drug Reaction

Adverse drug reaction	Atracurium	Cisatracurium
Bradycardia	2(5%)	0
Tachycardia	5(12.5%)	3(7.5%)
Hypertension	2(5%)	1(2.5%)
Hypotension	5(12.5%)	0
Flushing	2(5%)	0
Wheezing	2(5%)	1(2.5%)
Bronchial secretion	1(2.5%)	0
Bronchospasm	2(5%)	1(2.5%)
Erythema	6(15%)	4(10%)
Itching	1(2.5%)	0
Urticaria	4(10%)	1(2.5%)
Injection reaction	3(7.5%)	1(2.5%)

The numbers of ADR within atracurium group was higher than cisatracurium group

Reference: IOSR Journal of Dental and Medical Sciences; 17(3); PP 51-52.

Study Conclusion…

In patients with instability in hemodynamic parameters the cisatracurium was the appropriate choice.

Reference: IOSR Journal of Dental and Medical Sciences; 17(3); PP 51-52.

Cisatracurium Vs. Vecuronium Clinical Trials

Acute respiratory distress syndrome (ARDS)

Characterized by hypoxemic (low blood oxygen) respiratory failure; it affects both medical and surgical patients.

ARDS has been fatal in 40 to 60% of patients.

Current guidelines indicate that NMBA are appropriate for facilitating mechanical ventilation when sedation alone is inadequate, most notably in patients with severe gas-exchange impairments.

Reference: N Engl J Med 2010; 363:1107-1116

Multi-organ Dysfunction Patients

An Observational Study of the Efficacy of Cisatracurium Compared with Vecuronium in Patients with or at Risk for Acute Respiratory Distress Syndrome

Peter D. Sottile[1], Tyree H. Kiser[2], Ellen L. Burnham[1], P. Michael Ho[3], Richard R. Allen[4], R. William Vandivier[1], and Marc Moss[1]; for the Colorado Pulmonary Outcomes Research Group (CPOR)

[1]Division of Pulmonary Sciences and Critical Care Medicine and [3]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado; [2]Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy, Aurora, Colorado; and [4]Peaks Statistical Consulting, Evergreen, Colorado

Am J Respir Crit Care Med Vol 197, Iss 7, pp 897–904, Apr 1, 2018

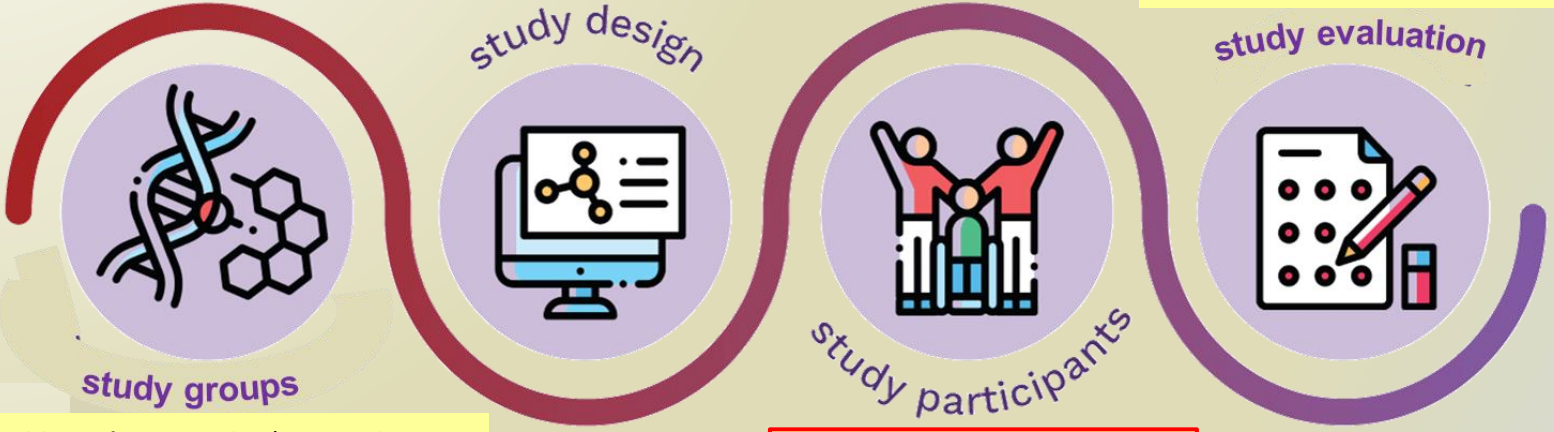
The study aimed to determine whether cisatracurium is associated with improved outcomes when compared with vecuronium in patients at risk for and with acute respiratory distress syndrome (ARDS).

Reference: Am J Respir Crit Care Med.2018;197(7):897–904.

Study Methodology…

Multicenter, observational cohort study

Outcomes included hospital mortality, duration of mechanical ventilation, ICU and hospital duration, and discharge location.



1901 patients: received vecuronium
1901 patients: received cisatracurium for intubation.

N= 3,802
(Cis - 54.3 6 16.2 vs. Vec- 50.8 6 17.1 yr;) patients

Reference: Am J Respir Crit Care Med.2018;197(7):897–904.

Study Results…

Patients treated with cisatracurium experienced fewer mechanical ventilator days (OR, 1.01; 95% CI, 0.30–1.72; P = 0.005)

Patients treated with cisatracurium experienced fewer ICU days (OR, 0.98; 95% CI, 0.11–1.86; P = 0.028) compared with patients treated with vecuronium.

Reference: Am J Respir Crit Care Med.2018;197(7):897–904.

Study Conclusion…

When compared with vecuronium, cisatracurium was associated with improved outcomes for patients at risk for and with ARDS. Therefore, **cisatracurium** may be the neuromuscular blockade **agent of choice for these patients**.

Reference: Am J Respir Crit Care Med.2018;197(7):897–904.

Cisatracurium Vs. Placebo Clinical Trial

Safety Profile

CLINICAL TRIAL V

ACURASYS Trial

ARDS

Prospective randomized study

Efficacy of both the drugs was compared in terms of onset of action, duration of action, duration of recovery, hemodynamic conditions during and after intubation, and signs of histamine release in both the drugs.

Cisatracurium besylate (N=178) (150-mg) Placebo (N=162).
A 3-ml rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered, followed by a continuous infusion of 37.5 mg per hour for 48 hours.

N= 340 patients

Reference: N Engl J Med. 2010 Sep 16;363(12):1107-16.

Study Results…

Efficacy Profile

In patients with severe ARDS, early administration of cisatracurium improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness.

Safety Profile

Bradycardia developed during the cisatracurium infusion in 1 patient. No other side effects were reported.

Reference: N Engl J Med. 2010 Sep 16;363(12):1107-16.

Cisatracurium In Critically ill Patients Clinical Trial

Critically ill Patients

Considerations in Neuromuscular Blockade in the ICU: A Case Report and Review of the Literature

Jessica D. Workum,[1,2] Stephanie H.V. Janssen,[1,3] and Hugo R.W. Touw[1]

Received	Revised	Accepted	Published
01 Jan 2020	09 Feb 2020	13 Feb 2020	07 Mar 2020

Reference: Jessica D. Workum et al. Considerations in Neuromuscular Blockade in the ICU: A Case Report and Review of the Literature. Case Reports in Critical Care, vol. 2020; 4.

Study Conclusion…

This case illustrates the complex pharmacokinetics of rocuronium in the critically ill, especially when administered as a continuous infusion, with an unexpectedly prolonged clinical effect. Combined with the recent findings of the ROSE trial, we strongly advise to exercise restrained use of continuous neuromuscular blockade in the ICU in general and advise to consider using intermittent boluses instead. If, however, the choice has been made to start continuous neuromuscular blockade, we strongly advise to monitor TOF levels during continuous infusion and after cessation of the drug. We furthermore advise to choose cisatracurium over a steroid-based NMBA like rocuronium in these situations, due to their more favorable pharmacokinetics in critically ill patients.

Reference: Jessica D. Workum et al. Considerations in Neuromuscular Blockade in the ICU: A Case Report and Review of the Literature. Case Reports in Critical Care, vol. 2020; 4.

Cisatracurium In Major Surgery Clinical Trial

Original Article

Gland Surg 2021;10(7):2150-2158 | https://dx.doi.org/10.21037/gs-21-109

Dosage effect of cisatracurium on intubation and intraoperative neuromonitoring during thyroidectomy: a randomized controlled trial

Xiaoxi Li[1], Bin Zhang[2], Guohui Xu[2], Yuntao Song[2], Ling Yu[1], Jiaonan Yang[1], Hongyu Tan[1]

Intraoperative neuro-monitoring (IONM) reduces the risk of recurrent laryngeal nerve (RLN) injury during thyroid surgery. However, the use of neuromuscular blocking agents (NMBAs), which are essential to improve intubation conditions, may hinder the electro-myographic response during IONM.

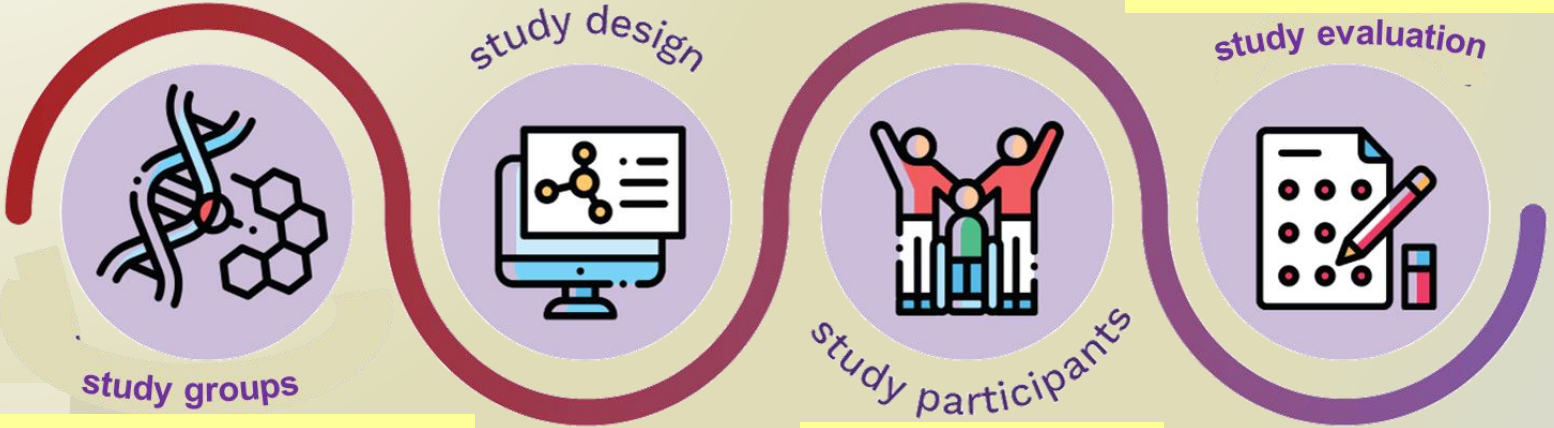
The study aimed to explore the optimal dosage of cisatracurium to produce adequate muscle relaxation for tracheal intubation without significantly affecting evoked potentials of Intraoperative neuro-monitoring (IONM) during thyroidectomy.

Reference: Gland Surg 2021;10(7):2150-2158.

Study Methodology…

Prospective, double-blind, randomized controlled trial

Ease of intubation was evaluated with the intubation condition score (Cooper score) and the intubation difficulty scale (IDS).
Amplitudes of evoked potentials during intermittent IONM were compared between groups.



Cisatracurium (0.05 mg/kg in group C1 and 0.1 mg/kg in group C2) (prepared in a 10-mL syringe with an equal volume of normal saline)

N= 52 patients

Reference: Gland Surg 2021;10(7):2150-2158.

Study Results…

Data regarding the intubation process

Variable	Group C1 (n=26)	Group C2 (n=26)	Statistics	P
Cooper score	8.0 (7.0–8.3)	9.0 (9.0–9.0)	4.799†	<0.001***
Cormack-Lehane grade III/IV	16 (61.5)	3 (11.5)	14.016‡	<0.001***
Required assistance	16 (61.5)	4 (15.4)	11.700‡	0.001**
IDS score	3.0 (0.0–4.0)	1.0 (0.0–1.0)	2.001†	0.045*
Intubation time (s)	42.5 (33.0–50.0)	35.0 (29.8–40.0)	2.090†	0.037*

Data are presented as median (interquartile range) or n (%). Group C1, patients intubated with 1× ED_{95} (0.05 mg/kg) of cisatracurium; Group C2, patients intubated with 2× ED_{95} (0.1 mg/kg) of cisatracurium. †, Z value; ‡, chi-square value; *, P<0.05; **, P<0.01; ***, P<0.001. IDS, intubation difficulty scale.

There were no significant differences between group C1 and group C2 regarding preoperative airway evaluation. **All patients in both groups were successfully intubated.**

Reference: Gland Surg 2021;10(7):2150-2158.

Study Results…

Intubation-related postoperative complications

Variable	Group C1 (n=26)	Group C2 (n=26)	χ^2	P
Blood-tinged sputum during extubation	5 (19.2)	3 (11.5)	–	0.703
Sore throat	6 (23.1)	6 (23.1)	0.000	1.000
Odynophagia	8 (30.8)	7 (26.9)	0.094	0.760
Hoarseness	2 (7.7)	0 (0.0)	–	0.490

Data are presented as n (%). Group C1, patients intubated with 1× ED_{95} (0.05 mg/kg) of cisatracurium; Group C2, patients intubated with 2× ED_{95} (0.1 mg/kg) of cisatracurium.

No serious adverse events were observed.

Odynophagia: Painful swallowing

Reference: Gland Surg 2021;10(7):2150-2158.

Study Conclusion…

Cisatracurium provided better intubation conditions and easier tracheal intubation.

Reference: Gland Surg 2021;10(7):2150-2158.

Cisatracurium in Elderly Patients Clinical Trial

Cisatracurium Clinical Trials In Elderly patients

CLINICAL TRIAL I

Cisatracurium was appropriate for elderly patients because of its more rapid activation and low variability in the recovery index. - **Korean J Anesthesiol. 2016 Oct; 69(5): 453–459.**

CLINICAL TRIAL II

The range of inter patient variability that neuromuscular blocking drugs may exhibit is then considered and drugs with a narrower range, such as cisatracurium, may produce more predictable & inherently safer, outcomes.

- **Journal of Pain Research 2016:9 437–444**

CLINICAL TRIAL III

We hold the opinion that cisatracurium is safer in elderly patients - **Anesth Pain. 2013;2(4):142-148.**

Reference: BMC Anesthesiol 14, 29 (2014). https://

Cisatracurium: Summary

- **The duration of action of cisatracurium is longer than that of atracurium.** [1]
- Less cisatracurium is required to achieve a given degree of neuromuscular blockade and so **less laudanosine (metabolite that crosses blood brain barrier and can cause convulsions) is produced.**[1]
- **Does not trigger histamine release.**[2]
- **No increase in ICU-acquired weakness.**[4]
- **Lower duration of mechanical ventilation & ICU length of stay.**[4]
- **Preferred NMBA for patients at risk for and with ARDS.**[3]
- **Higher dose is safe and more efficacious.**[5]
- **Faster recovery and without any residual muscle paralysis.**[5]
- **Use in patients with multi-organ dysfunction and with an increased risk of death.**[6]
- **Cisatracurium is suitable for the elderly** because it acted quickly. Also, cisatracurium is appropriate for elderly patients because of its more rapid activation and low variability in the recovery index.[7]
- **Cisatracurium was administered** when indicated according to the international clinical practice guidelines **for the sustained neuromuscular blockade in the adult critically ill patient.**[8]

Reference: 1. Cisatracurium overview as accessed on 27th July, 2021- https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/cisatracurium ; 2..Sparr, H.J., et al. Newer Neuromuscular Blocking Agents. Drugs.2001;61:919–942.; 3.Sottile PD et al. Am J Respir Crit Care Med. 2018;197(7):897–904; 4. Hraiech S et al. Intensive Care Med. 2020;46:2357–2372.; 5. Rochana G Bakhshi et al. JMSCR. December 2016;4(12):14613-14621; 6. Am J Respir Crit Care Med.2018;197(7):897–904.; 7.Korean J Anesthesiol. 2016 Oct; 69(5): 453–459.; 8.Crit Care Med. 2016;44:2079–103.

Rapid-Sequence Intubation (RSI)

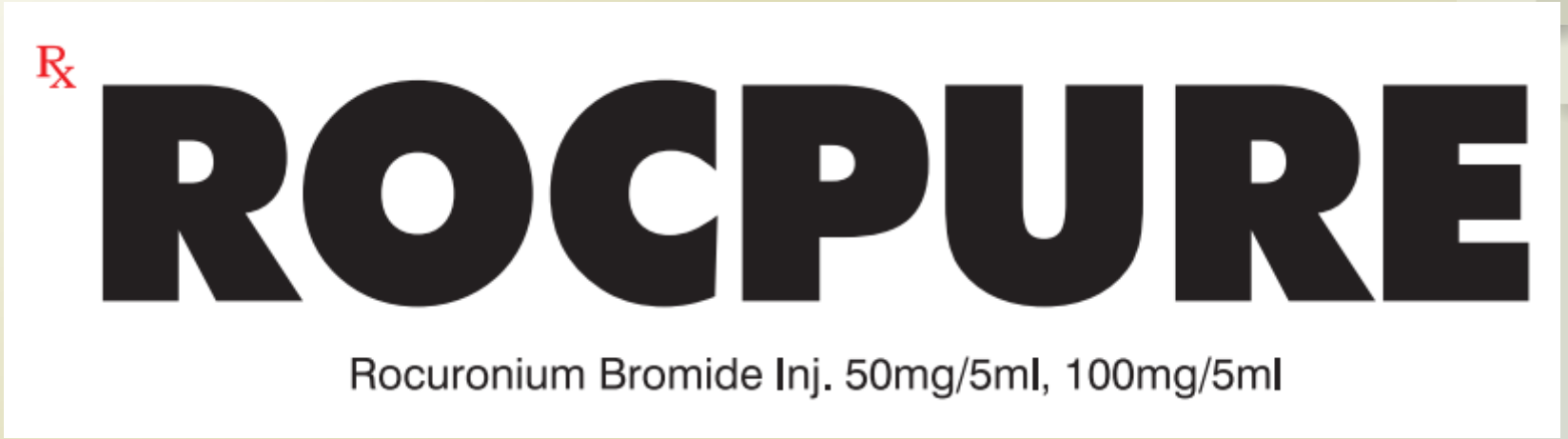
- This technique secures the airway of an unprepared patient, who is at risk for aspiration of gastric contents, in an immediate and safe manner.[1]
- Rapid-sequence induction is documented to be a safer technique than either nasotracheal intubation or orotracheal intubation.[1]
- It involves loss of consciousness during cricoid pressure followed by intubation without face mask ventilation. [2]

RSI VIDEO: https://www.youtube.com/watch?v=0PQhseOdFNQ

Reference: 1. Patrick M. Kochanek, et al. Chapter 61 - Severe Traumatic Brain Injury in Infants and Children. Pediatric Critical Care (4th Edition),2011;849-870. 2. Continuing Education in Anaesthesia Critical Care & Pain,. 2005;5(2):45–48,

Rapid Sequence Intubation

INTRODUCING



Rocuronium: Introduction

- Rocuronium bromide (rocuronium) is a relatively low-potent, intermediate-acting neuromuscular blocking agent (NMBA).
- Its main advantage is the rapid onset of neuromuscular block whereby good or excellent intubating conditions are achieved within 60 to 90 seconds.
- Larger doses of rocuronium (≥1 mg/kg) seem to be suitable for rapid-sequence induction under relatively light anesthesia.
- Does not release histamine, even when administered in large doses.
- Unlike vecuronium, rocuronium has no metabolite.

Reference: Sparr, H.J., et al. Newer Neuromuscular Blocking Agents. Drugs.2001;61:919–942.

Rocuronium: Product Profile

Approval in India: June 1996

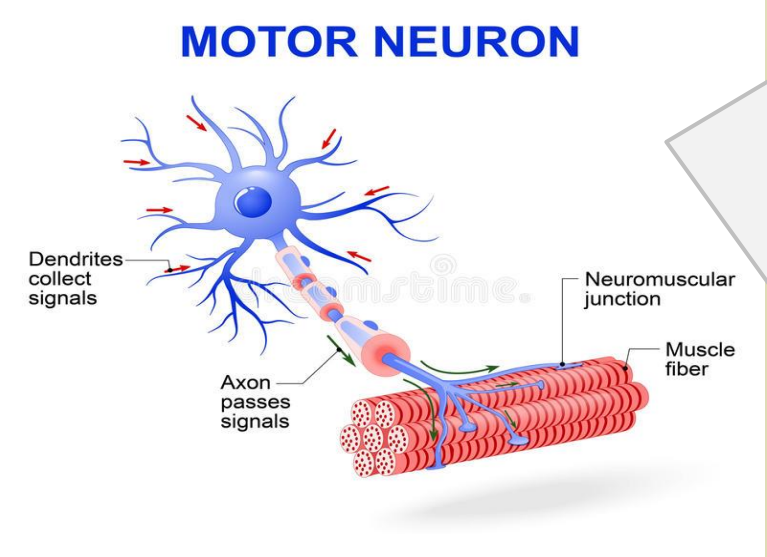
Strength: Rocuronium bromide inj.-50mg/5ml, 100mg/10ml

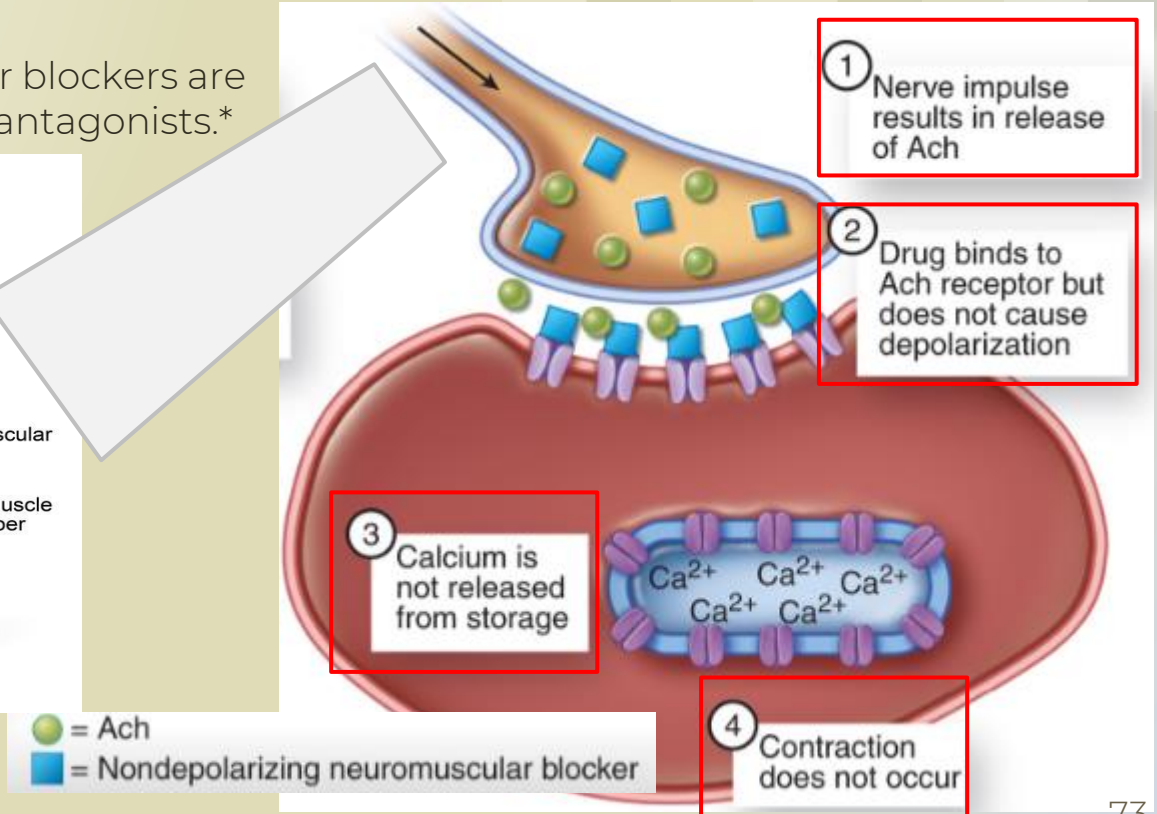
Approved Indications: As an adjuvant to general anesthesia to facilitate endotracheal incubation to provide skeletal muscle relaxation during surgery.

Reference: As accessed on 27th July 2021 - https://cdscoonline.gov.in/CDSCO/Drugs

Rocuronium: Mechanism of Action

- Non-depolarizing neuromuscular blockers are competitive acetylcholine (ACh) antagonists.*





Reference: https://biology-forums.com/index.php?action=gallery;sa=view;id=28462 . * Cook D, Simons DJ. Neuromuscular Blockade. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538301/

Rocuronium: Dosage & Administration

Tracheal Intubation in Adults

Initial dose is 0.6 mg/kg.
Rapid sequence intubation: 0.6 to 1.2 mg/kg.

Maintenance Doses

Guided by response to prior dose, not administered until recovery is evident. Recommended **0.1, 0.15, and 0.2 mg/kg**.

Continuous infusion

Initial rate of 10 to 12 mcg/kg/min. Start only after early evidence of spontaneous recovery from an intubating dose.

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Dosage & Administration

Tracheal Intubation in Pediatric Patients

The recommended **initial intubation dose is 0.6 mg/kg**; however, a lower dose of 0.45 mg/kg may be used depending on anesthetic technique and the age of the patient.

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Pharmacokinetics

Elimination half life: 1.4 hrs in adults and 1.5 hrs in geriatric patients.

Plasma protein binding: Rocuronium is approximately 30% bound to human plasma proteins.

Elimination: Primarily eliminated by liver

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Contraindications

Hypersensitivity (e.g., anaphylaxis) to rocuronium bromide or other neuromuscular blocking agents.

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Safety Profile

Most common adverse reactions (2%) are transient hypotension and hypertension

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Use in Special Populations

❖ Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

Rocuronium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

❖ Labor and Delivery

The use of Rocuronium in Cesarean section has been studied in a limited number of patients.

It is not recommended for rapid sequence induction in Cesarean section patients.

❖ Breast-feeding*

It is unknown whether rocuronium bromide is excreted in human breast milk.

Reference: International PI US, Reference ID: 2867727. ; * International PI UK, 05/06/2020. As accessed on -1/10/2021- https://www.medicines.org.uk/emc/product/553/smpc#gref

Rocuronium: Use in Special Populations

❖ Pediatric Use

Rocuronium is not recommended for rapid sequence intubation in pediatric patients.

❖ Geriatric Use

No differences in duration of neuromuscular blockade following maintenance doses of Rocuronium were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Use in Special Populations

❖ Patients with Hepatic Impairment

Since Rocuronium is primarily excreted by the liver, **it should be used with caution in patients with clinically significant hepatic impairment.**

If used for rapid sequence induction in patients with ascites, an increased initial dosage may be necessary to assure complete block. Duration will be prolonged in these cases.
The use of doses higher than 0.6 mg/kg has not been studied.

❖ Patients with Renal Impairment

In patients with renal dysfunction, the duration of NMB was not prolonged; however, there was substantial individual variability (range: 22-90 minutes)

Reference: International PI US, Reference ID: 2867727.

Rocuronium: Clinical Trials in RSI

Rocuronium appears to be the safest drug, near to **ideal NMBA for RSI** and routine intubation when there is no anticipated difficulty in intubation. [1]

Time required for intubation was statistically **significantly shorter in the rocuronium group.**[2]

Rocuronium bromide is a safe alternative to succinylcholine chloride for RSI in adult patients. [3]

Significantly shortened the onset of relaxation and the timing of intubation compared to vecuronium.[2]

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.; 2. Egyptian Journal of Anaesthesia. 2020;36(1,):05-111.; 3. International Journal of Contemporary Medical Research. 2016;3(3):700-703.

Rocuronium Vs. Vecuronium Clinical Trials

Indications

Rapid Onset of Action

Longer Duration of Action

Optimal intubation

Better Hemodynamic Profile

Safety Profile

INDIAN TRIAL

Tracheal Intubation & RSI

Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - 1): 161-167
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.23

Rocuronium Versus Vecuronium in Endotracheal Intubation and Maintenance in General Anaesthesia

D. Srinivasa Naik[1], K. Ravi Kumar[2]

Adequate maintenance of airways in patients undergoing surgeries under general anesthesia was through proper intubation. Succinylcholine was the most opted neuromuscular drug in the past 50 years administered for tracheal intubation. A number of adverse reactions with its use.

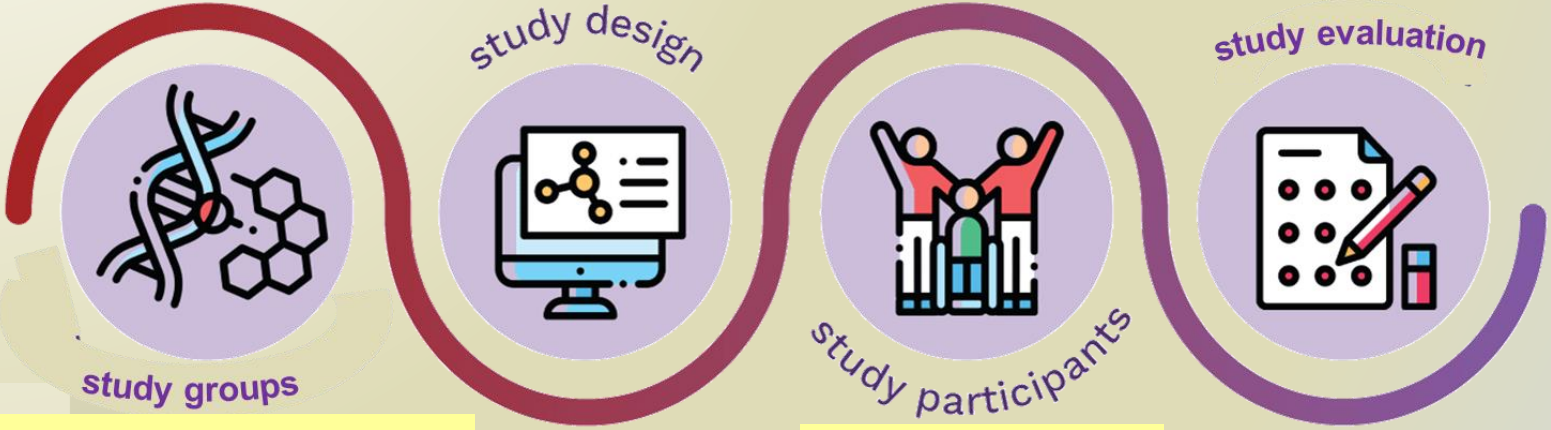
The study aimed to evaluate onset time, tracheal intubation conditions, duration of action and maintenance of anesthesia using two none depolarizing muscle relaxants vecuronium and rocuronium

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.

Study Methodology…

Randomized, prospective clinical double blinded trial studied over a period of 2 years

In both the groups, the efficacy of non-depolarizing muscle relaxant was assessed.



Patients in group rocuronium (R): received rocuronium (0.6 mg/kg)
Patients in group vecuronium (V): received vecuronium (0.1 mg/kg).

N= 50 patients

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.

The Study Evaluated

Cooper Scoring System

Score	Jaw relaxation	Vocal cords	Response to intubation
0	Impossible to open	Closed/ bucking	severe coughing
1	Opens with difficulty	Closing	Mild coughing
2	Moderate opening	Moving movement	Slight diaphragmatic
3	Easy opening	Open [relaxed]	No movement

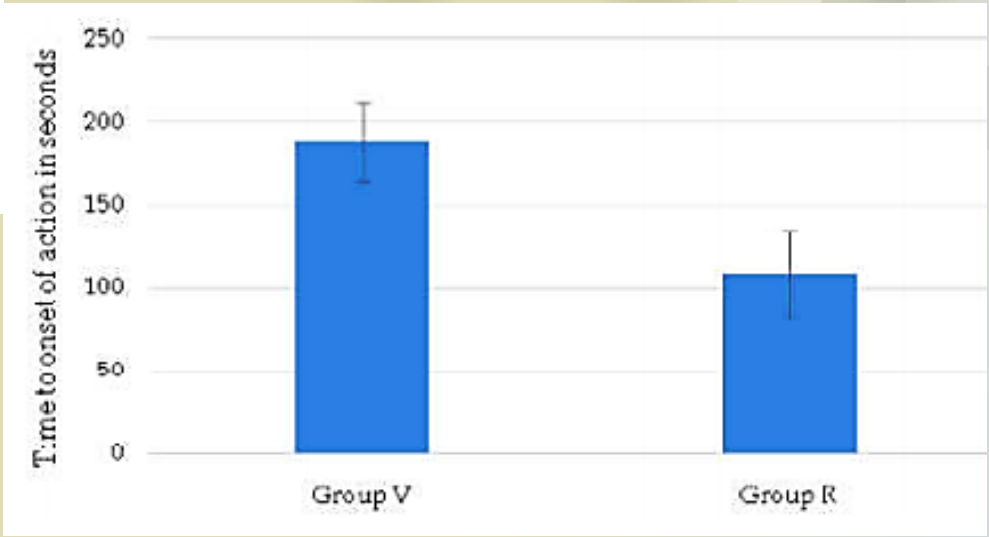
Intubating condition were scored as excellent [8-9], good [6-7], fair [3-5], and poor [0-2] according to a system described by Cooper.

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.

Study Results…

Cooper score in relation to onset of Action

Seconds	Rocuronium	SD	Vecuronium	SD
0	0		0	
30	1.12	0.44	0.72	0.46
60	1.88	0.53	1.04	0.20
90	2.46	0.59	1.6	0.50
120	2.83	0.50	1.88	0.33
180	3	0.00	2.6	0.58
240			3	0.66
300			2.67	
360				



- **Onset of action and cooper scoring for adequacy for intubation** it was found that in the present study in **Group R score of more than 2.5 was achieved by the 120th second** whereas in Group V only 1.8 was achieved in 120th second.
- This shows the **rapid onset of group R over Group V.**

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.

Study Conclusion…

- Rocuronium has a significantly rapid onset of action and intermediate duration of action. It is easily reversible and produces no significant cardiovascular changes. It also has a good safety profile.

- **Rocuronium appears to be the safest drug, near to ideal NMBA for rapid sequence intubation and routine intubation when there is no anticipated difficulty in intubation.**

Reference: Indian Journal of Anesthesia and Analgesia. 2019; 6(1) (Part - 1): 161-167.

Rocuronium Vs. Vecuronium In RSI-sub group

CLINICAL TRIAL II

RSI In Morbidly Obese Patients

EGYPTIAN JOURNAL OF ANAESTHESIA
2020, VOL. 36, NO. 1, 105–111
https://doi.org/10.1080/11101849.2020.1783179

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Comparison of vecuronium or rocuronium for rapid sequence induction in morbidly obese patients: a randomized study

Mohamed M. Abu Yazed and Sameh Abdelkhalik Ahmed

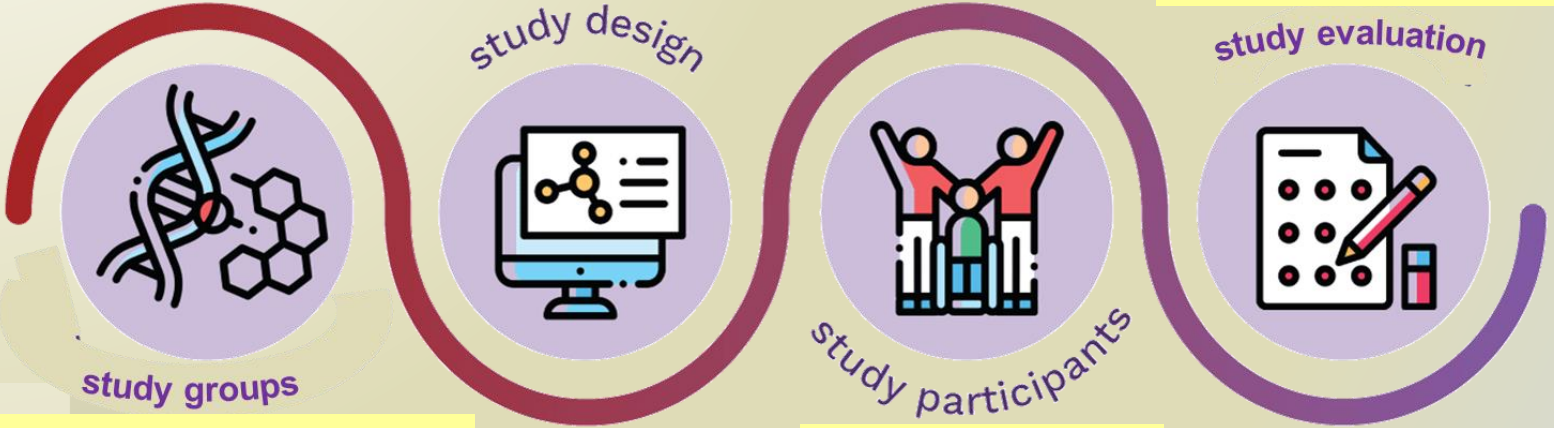
This trial aimed to evaluate the effect of the use of triple the ED95 of rocuronium and vecuronium on the onset of relaxation and the intubation score in morbidly obese patients.

Reference: Egyptian Journal of Anaesthesia. 2020;36(1,):05-111.

Study Methodology…

Randomized, double-blind clinical trial

The onset and duration of relaxation, the time of intubation, and the intubation scores were assessed.



ROC group, in which patients received rocuronium (0.9 mg/kg).
VEC group, in which the patients received vecuronium (0.15 mg/kg).

N= 60 patients

Reference: Egyptian Journal of Anaesthesia. 2020;36(1,):05-111.

Study Results…

Timing and duration of relaxation

	ROC group	VEC group	P
Onset of relaxation (Sec)	57.5 ± 19.9	105.0 ± 18.8	<0.0001*
Time for Intubation (Sec)	69.00 ± 19.4	120.8 ± 17.7	<0.0001*
Duration of relaxation (min)	85.5 ± 19.2	72.00 ± 22.65	0.016*
Intubation Score			0.656
Excellent	13 (43.3%)	10 (33.33%)	
Good	16 (53.3%)	18 (60.0%)	
Poor	1(3.33%)	2 (6.67%)	
Inadequate	0 (0%)	0 (0%)	

- **Onset of relaxation was significantly shorter in the rocuronium group** than in the vecuronium group.
- **Time required for intubation was statistically significantly shorter in the rocuronium group** than in the vecuronium group.
- **Duration of relaxation was statistically significantly longer in the rocuronium group** than in the vecuronium group.

Reference: Egyptian Journal of Anaesthesia. 2020;36(1,):05-111.

Study Conclusion…

The use of rocuronium in morbidly obese patients significantly shortened the onset of relaxation and the timing of intubation compared to vecuronium.

Reference: Egyptian Journal of Anaesthesia. 2020;36(1,):05-111.

CLINICAL TRIAL III

In Surgeries Under General Anesthesia

International Journal of Medical Science and Public Health I 2016 I Vol 5 I Issue 08 1617

Research Article

Comparison of hemodynamic and neuromuscular properties of rocuronium versus vecuronium in anesthesia

Umamaheswara Rao

Adequate maintenance of airways in patients undergoing surgeries under general anesthesia was through proper intubation. This was achieved by the extensive usage of neuromuscular blocking drugs, which provided good intubation conditions and relaxation of the muscles. Neuromuscular blockers play a key role in general anesthesia. Rocuronium and vecuronium are used as nondepolarizing muscle relaxants.

The trial aimed to study the neuromuscular properties and cardiovascular effects of rocuronium bromide, the "near-ideal" muscle relaxant and to compare it with vecuronium bromide, an already established drug, during anesthesia.

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

Study Methodology…

Prospective randomized double-blinded study

Hemodynamic parameters such as systolic blood pressure (BP), diastolic BP, and heart rate were recorded at base line during preoxygenation and at 1, 3, 5, and 10 min after induction.

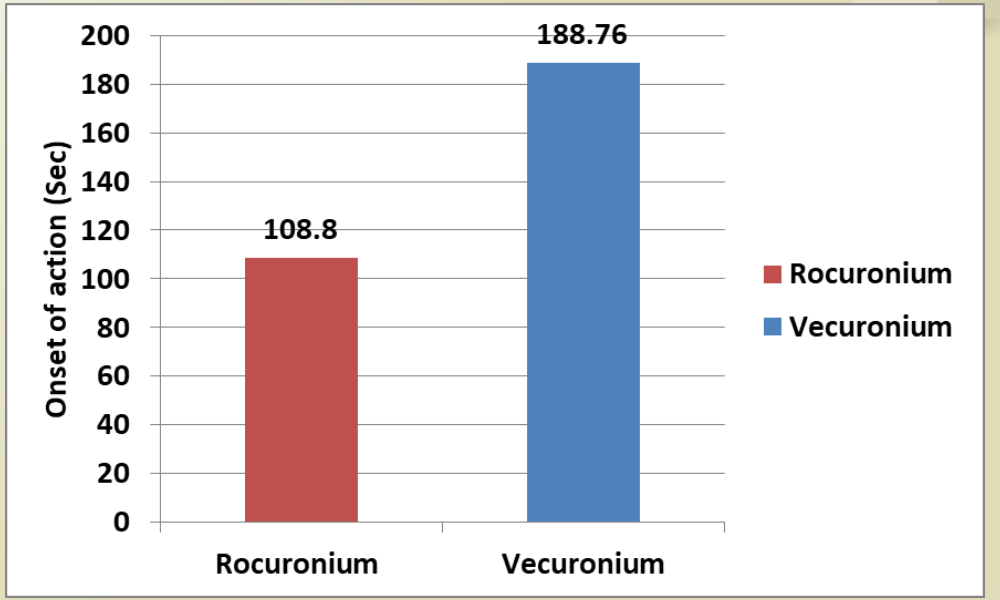
25 patients received 0.6 mg/kg of rocuronium bromide. Other 25 patients received 0.1 mg/kg of vecuronium bromide. The top-up doses administered were 0.15 mg/kg of rocuronium and 0.025 mg/kg of vecuronium.

N= 50 patients

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

Study Results…

Onset of Action



The onset time was significantly shorter in the rocuronium group 108.8 sec compared with vecuronium group 188.76 sec.

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

Study Results…

Duration of action of initial and top-up doses

Doses	Group V		Group R	
	Mean (min)	SD	Mean (min)	SD
Initial dose	24.5	7.54	31.5	8.9
First top-up	24.73	5.5	28.48	4.8
Second top-up	24.44	6.6	28.14	5.27
Third top-up	23.50	7.36	28.25	6.8
Fourth top-up	20.50	6.65	31.50	2.12
Fifth top-up	25	—	—	—

V, vecuronium; R, rocuronium; SD, standard deviation.

The duration of action between the two groups was that group R had a longer duration of action when compared with vecuronium and it also had a significant p value of 0.01.

The top-up doses also indicated that rocuronium seems to have a prolonged action than Vecuronium

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

Study Results…

Values of hemodynamic responses

Time	Heart rate		Systolic blood pressure		Diastolic blood pressure	
	Group V	Group R	Group V	Group R	Group V	Group R
0	85.84	84.96	128.16	129.04	81.84	84
2	85.52	83.60	131.36	128.48	83.76	85.92
4	83.76	81.96	132.96	129.20	84.48	87.76
6	82.84	81.60	130.88	126.40	82.88	86.40
8	80.64	82.12	128.40	126.72	80.80	83.92
10	78.60	81.44	128.08	125.20	81.44	81.68
15	78.20	79.88	170.28	165.20	81.76	81.52
20	77.84	78.48	125.76	126.16	82.72	81.92
25	79.56	77.16	124.16	128.16	83.04	81.04
30	78.88	80.52	124.24	126.48	82.80	81.68
45	77.88	80.52	125.44	123.28	81.92	82.00
60	77.36	80.40	124.56	122.16	80.72	80.24
75	79.04	79.68	125.28	123.92	80.64	81.04
90	77.80	79.64	124.80	122.96	81.04	80.96
105	79.36	81.24	124.72	123.36	80.96	80.32
120	79.20	80.28	126.16	124.32	80.24	81.92
360	78.80	76.80	124.88	126.88	80.80	82.64

V, vecuronium; R, rocuronium.

No changes in heart rate occurred with the given dose of rocuronium.

Also, throughout the study period, in rocuronium group the systolic BP remained between 122.16 mm of Hg and 128.16 mm of Hg. And the diastolic BP remained between 80.24 mm of Hg and 86.18 mm of Hg.

Rocuronium is associated with a high degree of cardio-stability

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

Study Conclusion…

Rocuronium has a significantly rapid onset of action and intermediate duration of action.

It is easily reversible and produces no significant cardiovascular changes. It also has a good safety profile.

Rocuronium appears to be a safe drug for rapid sequence intubation when there is no anticipated difficulty in intubation and also in surgeries of prolonged duration without any adverse cardiovascular effects.

Reference: International Journal of Medical Science and Public Health. 2016;5(08);1617-1620.

CLINICAL TRIAL IV

INDIAN TRIAL

In CABG

Published online: 2020-04-15

68 Original Article

THIEME OPEN ACCESS

Comparison of Rocuronium and Vecuronium in Patients Undergoing Elective Ultrafast-Track Off-Pump Coronary Artery Bypass Surgery (CABG)

Kalpana S. Shah[1] Aayush Kulshrestha[1]

[1]Department of Anaesthesia, Breach Candy Hospital, Mumbai, Maharashtra, India

Address for correspondence Aayush Kulshrestha, DNB, Room no. 22, Godrej Wing, Breach Candy Hospital, 60 A, Bhulabhai Desai Marg, Breach Candy, Cumballa Hill, Mumbai 400026, Maharashtra, India (e-mail: aayush.kul@gmail.com).

J Card Crit Care 2020;3:68–76

Neuromuscular blocking drugs are necessary in cardiac surgery to facilitate smooth intubation and ventilation conditions, avoid patient movement, reduce oxygen consumption, and prevent shivering.

Hemodynamic stability is very essential in cardiac surgery because the coronary reserve is below normal in such patients.

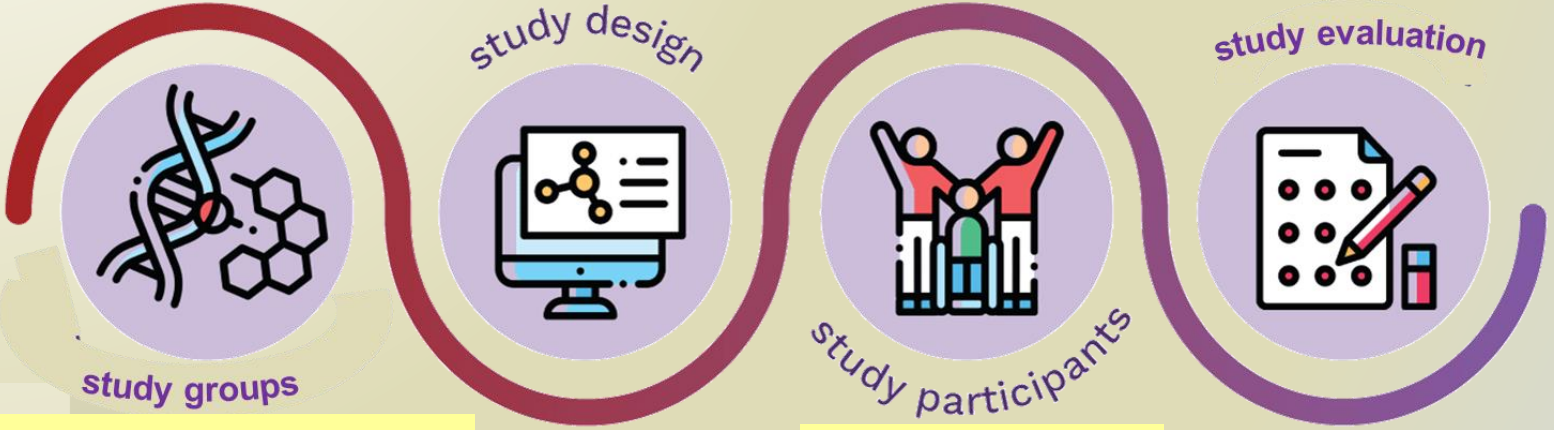
This study was conducted with the objective of comparing rocuronium, the "near-ideal" muscle relaxant with vecuronium, an already established neuromuscular blocking agent in patients undergoing elective ultrafast-track off-pump coronary artery bypass surgery (CABG).

Reference: J Card Crit Care 2020;3:68–76.

Study Methodology…

Prospective randomized comparative study

Intubating conditions and various hemodynamic parameters were observed at different time points.



Patients in group rocuronium (R): received rocuronium (0.6 mg/kg)
Patients in group vecuronium (V): received vecuronium (0.1 mg/kg).

N= 60 patients

Reference: J Card Crit Care 2020;3:68–76.

The Study Evaluated

Four-step scale proposed by Goldberg et al

Grade 1 (excellent): good jaw relaxation, vocal cords relaxed, and easy passage of the endotracheal tube without coughing.

Grade 2 (good): jaw well relaxed, vocal cords relaxed, and passage of the tube with slight cough.

Grade 3 (poor): passage of the tube with moderate coughing or bucking, some vocal cord movements.

Grade 4 (impossible): jaw not relaxed, vocal cords adducted or not visualized, and passage of the tube impossible.

Reference: J Card Crit Care 2020;3:68–76.

Study Results…

Comparison of grades of relaxation among the study groups

Grade of relaxation	Study groups	
	Group R	Group V
1	29	26
2	1	4

Comparing the grades of relaxation in both the study groups, 86.70% patients in group V had grade 1 relaxation and 13.3% had grade 2 relaxation.

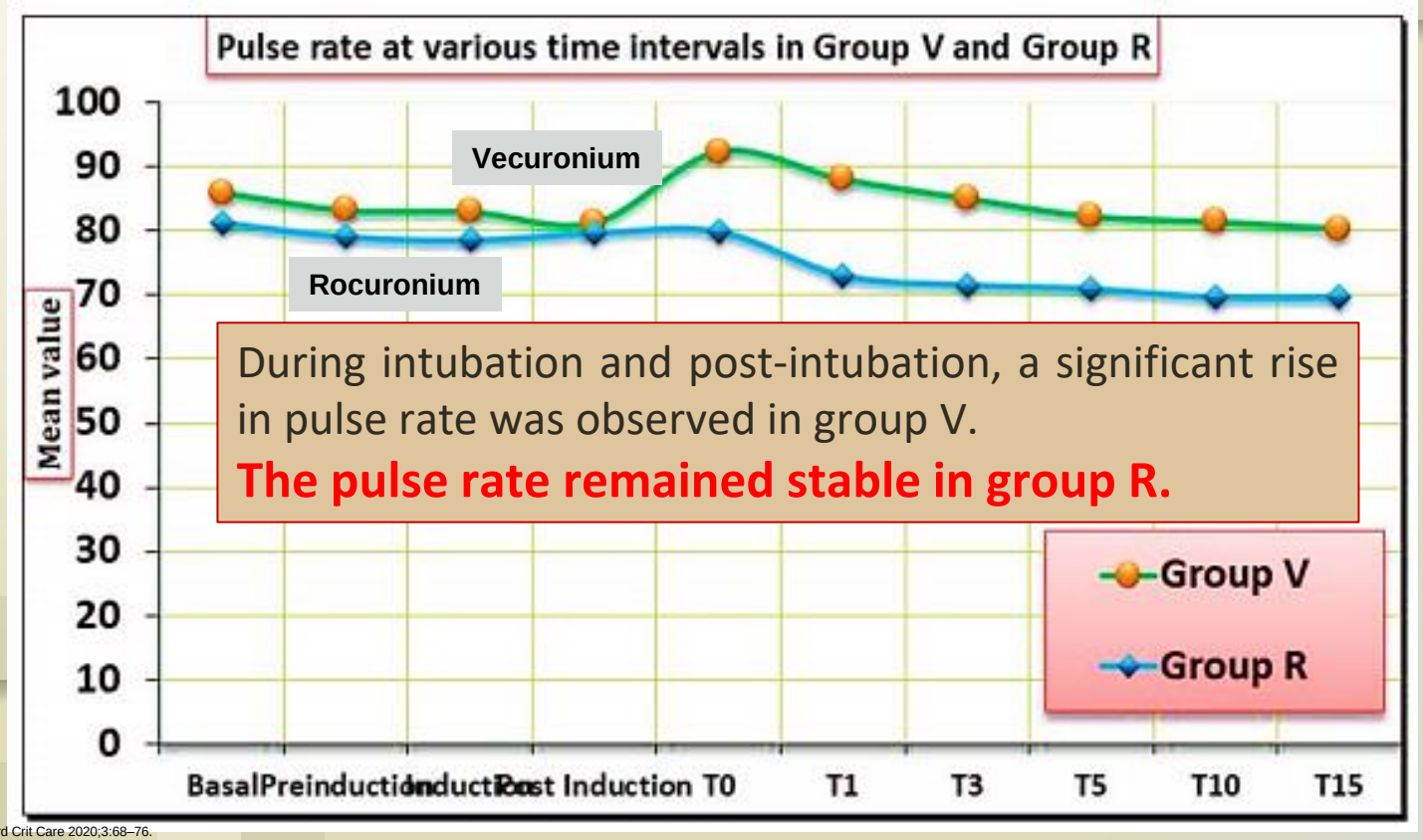
Group R, 96.70% patients had grade 1 and 3.30% had grade 2 relaxation.

None of the patients had grade 3 or 4 relaxation in both groups.

Reference: J Card Crit Care 2020;3:68–76.

Study Results…

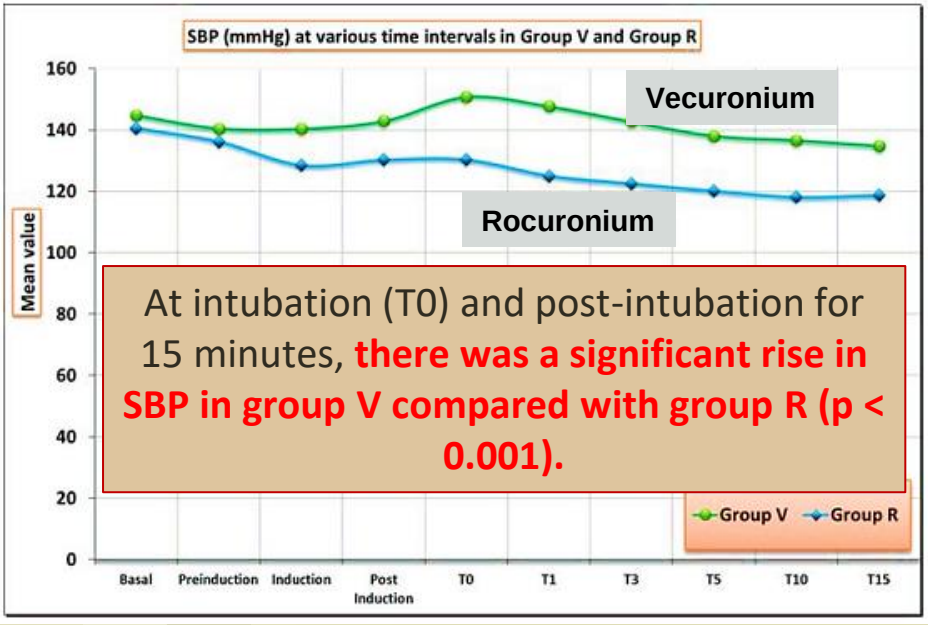
Pulse rate at various time and intervals in both groups



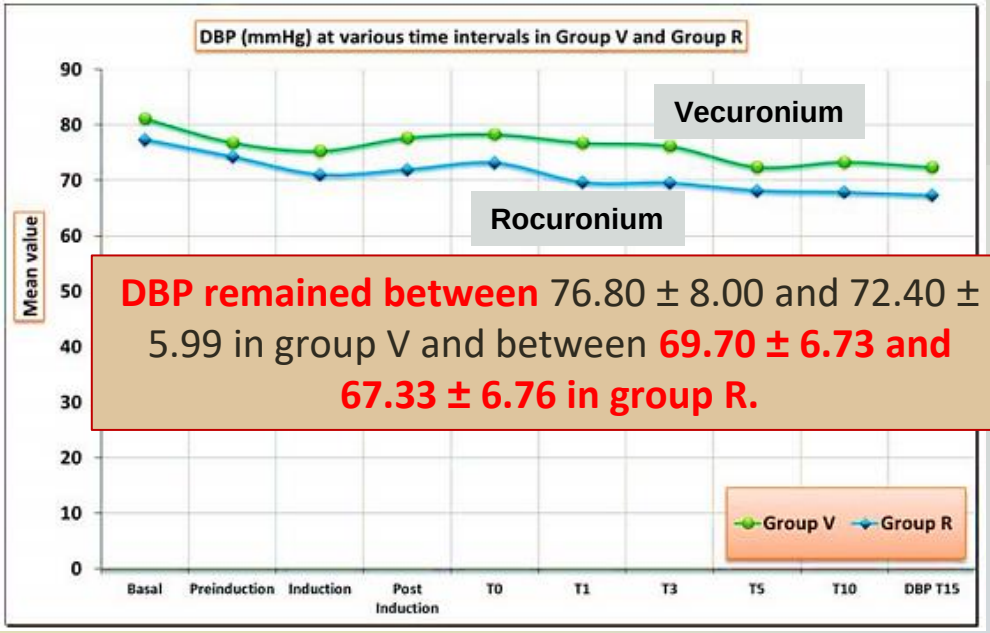
Reference: J Card Crit Care 2020;3:68–76.

Study Results…

Comparing the SBP & DBP in both groups



At intubation (T0) and post-intubation for 15 minutes, **there was a significant rise in SBP in group V compared with group R ($p < 0.001$).**

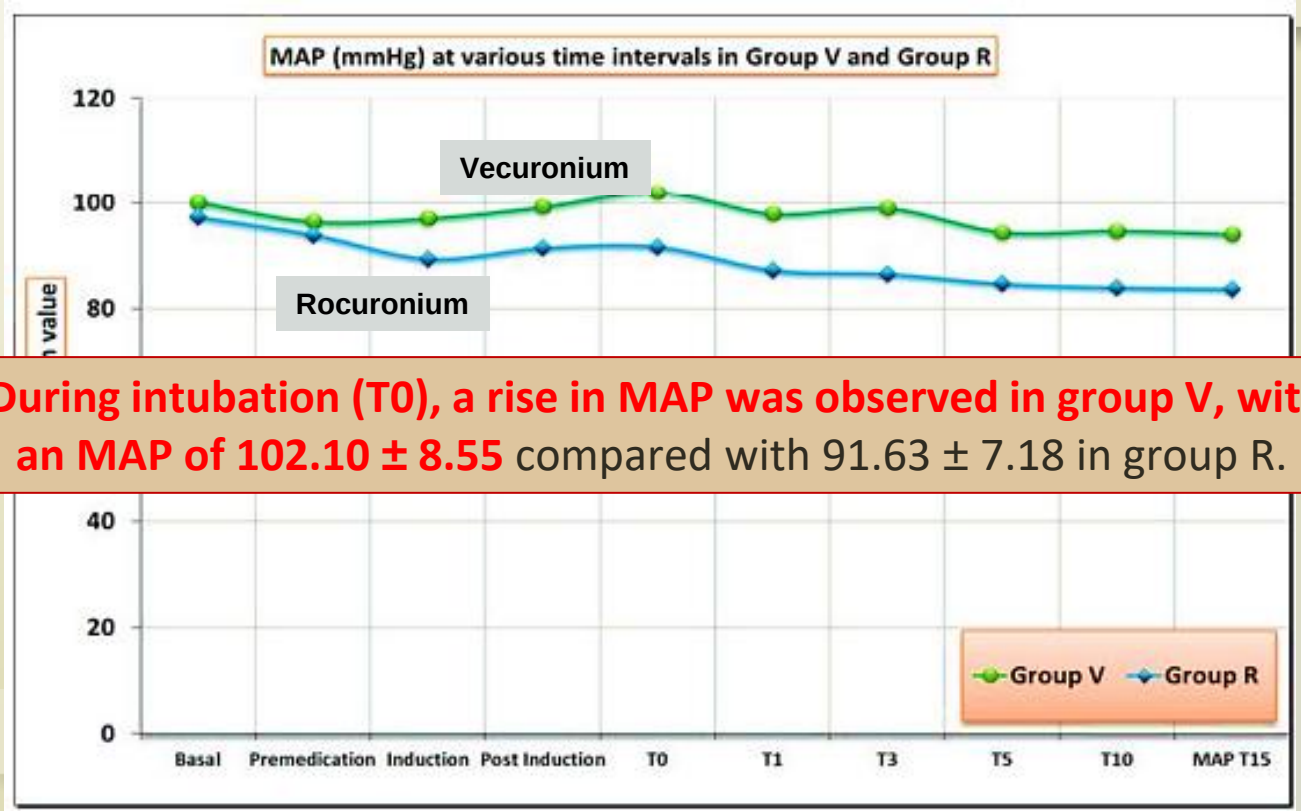


DBP remained between 76.80 ± 8.00 and 72.40 ± 5.99 in group V and between **69.70 ± 6.73 and 67.33 ± 6.76 in group R.**

Reference: J Card Crit Care 2020;3:68–76.

Study Results…

Comparing the MAP in both groups



During intubation (T0), a rise in MAP was observed in group V, with an MAP of 102.10 ± 8.55 compared with 91.63 ± 7.18 in group R.

Reference: J Card Crit Care 2020;3:68–76.

Study Conclusion…

Rocuronium provides good-to-excellent intubating conditions and is devoid of any significant cardiovascular changes causing hemodynamic instability when compared with vecuronium **in patients undergoing elective CABG.**

Reference: J Card Crit Care 2020;3:68–76.

CLINICAL TRIAL V

INDIAN TRIAL

In Cardiac Surgery

A Study of Hemodynamic Effects of Rocuronium Bromide and other Muscle Relaxants in Cardiac Surgery

Sanjay Kumar Gupta[1], Pooja Agarwal[2]

International Journal of Contemporary Medical Research | Section: Anesthesiology
ISSN (Online): 2393-915X; (Print): 2454-7379 | ICV: 98.46 | Volume 7 | Issue 2 | February 2020
B1

Use of muscle relaxants in cardiac surgery poses a challenge to anesthesia due to narrow margin of safety and limited cardiovascular function.

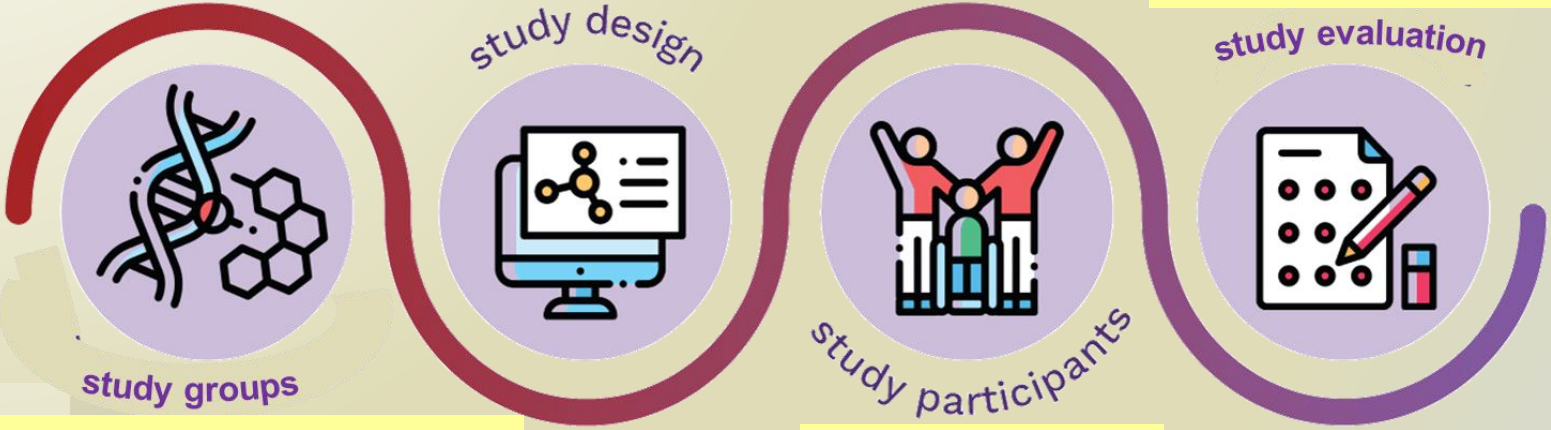
Therefore aim of present study is to find out the hemodynamic effects of Rocuronium bromide and other muscle relaxant in cardiac surgery.

Reference: International Journal of Contemporary Medical Research 2020;7(2):B1-B4.

Study Methodology…

Randomized, double-blind clinical trial

Muscle relaxants were given according to the group and hemodynamic parameters were recorded carefully at the interval of two, five and ten minutes.



Group A: Pancuronium bromide (20 patients)
Group B: Vecuronium bromide (20 patients)
Group C: Rocuronium bromide (20 patients)

N= 60 patients

Reference: International Journal of Contemporary Medical Research 2020;7(2):B1-B4.

Study Results…

Comparison of Hemodynamic Responses

Rocuronium has very stable hemodynamic profile.

Reference: International Journal of Contemporary Medical Research 2020;7(2):B1-B4.

Study Conclusion…

Rocuronium bromide is safer in cardiac surgery as compared to Vecuronium & Pancuronium.

Reference: International Journal of Contemporary Medical Research 2020;7(2):B1-B4.

Rocuronium Vs. Succinylcholine Clinical Trial

CLINICAL TRIAL VI

INDIAN TRIAL

RSI

International Journal of Contemporary Medical Research
Volume 3 | Issue 3 | March 2016 | ICV: 50.43 | ISSN (Online): 2393-915X; (Print): 2454-7379

Comparative Study of Rocuronium Bromide and Succinylcholine Chloride for Endotracheal Intubation During General Anesthesia

Madhavi Unmesh Santpur[1], Govind Marutrao Kahalekar[2], Priyanka Kanni[3], Bhargavi RSL[3]

Study Conclusion…

Rocuronium bromide is a safe alternative to succinylcholine chloride for rapid sequence induction in adult patients.

Reference: International Journal of Contemporary Medical Research. 2016;3(3):700-703.

Rocuronium: Summary

- Suitable alternative to succinylcholine during RSI. [1]
- Drug of choice in elective as well as emergency cardiac surgery.[2] And a safer option as compared to Vecuronium.[3]
- Renal failure does not affect the onset of rocuronium-induced neuromuscular blockade in adults or children.[4]
- Rocuronium-induced neuromuscular blockade can be readily and consistently reversed following the administration of reversal agents. [5]

Reference: 1. Santpur MU et al. Int J Contemp Med Res. 2016;3(3):700-703.; 2. Shah KS et al. J Card Crit Care 2020;3:68-76.; 3. International Journal of Contemporary Medical Research 2020;7(2):B1-B4.; 4.Rocuronium overview as accessed on 27th July, 2021- https://www.sciencedirect.com/topics/medicine-and-dentistry/rocuronium ; 5. Masui. 2006 Jul;55(7):826-33.

THANK YOU!

GLYCOPYRROLATE

ACETYLCHOLINE

Acetylcholine is a chief neurotransmitter of parasympathetic nervous system which is a part of autonomic nervous system.

Neurotransmitters- Chemical messengers Transmit a message (impulse) from one nerve to another, finally to target cell. (Target cell can be nerve cell/ muscle cell/ gland cell)

Nervous system can be broadly classified into two parts:

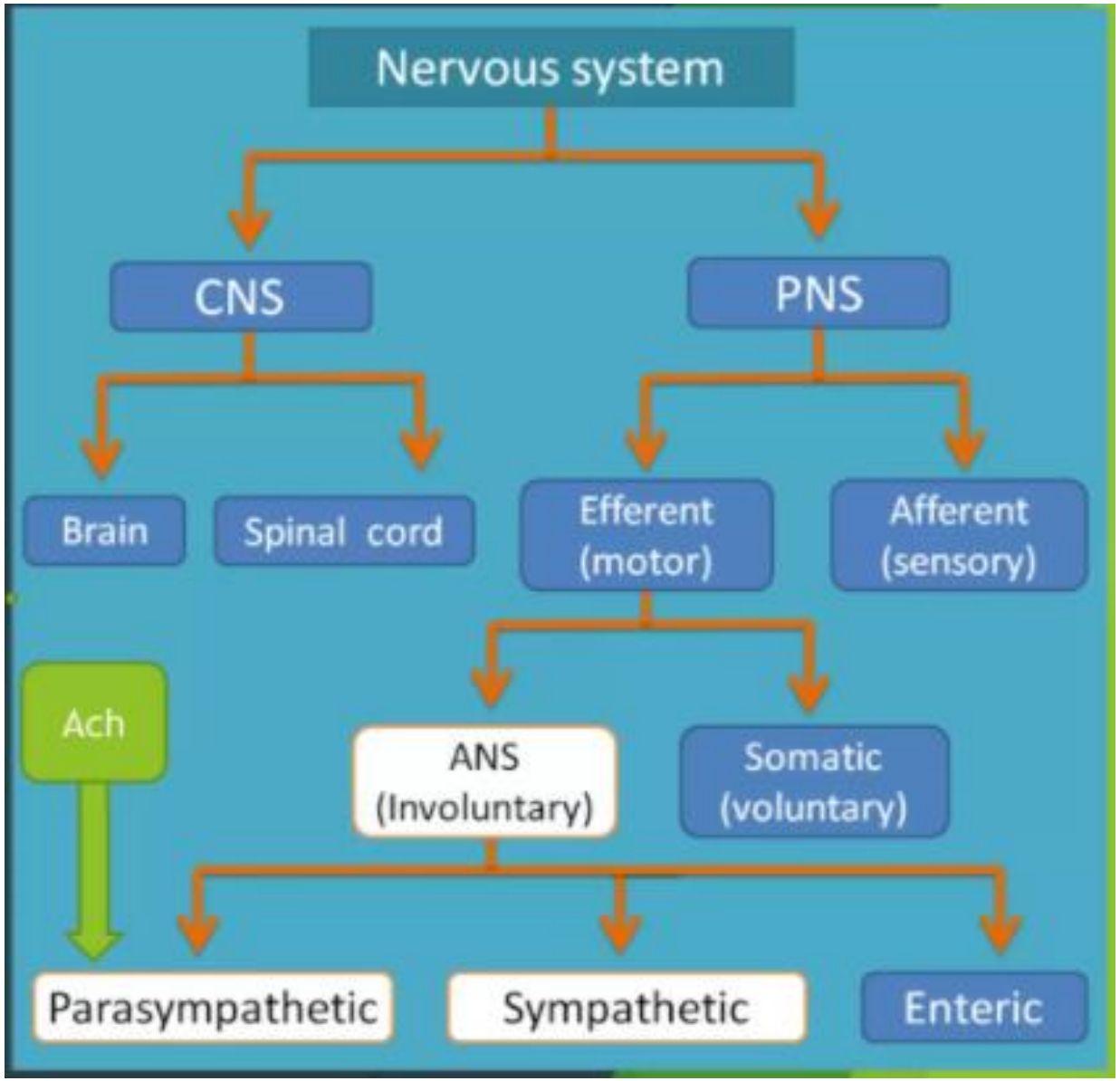
- CNS (central nervous system)
- PNS (peripheral nervous system)

PNS- Connects CNS to various organs

Efferent(Motor) neurons- Carry impulses away from CNS

Afferent (sensory) neurons- Carry impulses towards the CNS

Parasympathetic- Aka as Digest or rest system
Sympathetic- Aka Fight or flight system



ANTICHOLINERGIC DRUGS

Anti cholinergic drugs

Are those which antagonise the effect of neurotransmitter Acetylcholine (ACh) on autonomic effectors & in the CNS exerted through "Muscarinic receptors". Though nicotinic antagonists also block certain actions of Ach, they are referred to as "Ganglion blockers" & "Neuromuscular blockers"

Muscarinic receptor site-

- Heart
- Salivary glands
- Smooth muscles of GIT
- Genitourinary tract
- Urinary bladder

Muscarinic Receptor Subtypes

	M_1	M_2	M_3	M_4	M_5
Location	• CNS • Stomach	• Heart • CNS • Airway Smooth Muscle	• CNS • Salivary glands • Airway smooth muscle • Vascular endothelial cells	• CNS • Heart	• CNS
Clinical Effects	• Hydrogen Ion Secretion	• Bradycardia	• Salivation • Bronchodilation • Vasodilation	?	?
Clinically selective drugs available	Yes	No	No	No	No

Anticholinergics are drugs that oppose the effects of acetylcholine.

- In essence, they also lyse and block the effects of parasympathetic nervous system (PNS) so they are also called as parasympatholytics.

Nicotinic acetyl choline receptor site-

- Nerve endings of neuromuscular junction.

- Acetylcholine is also the neurotransmitter at postganglionic nicotinic receptors located at the NMJ (Neuromuscular junction) & autonomic ganglia.

- Effects of anticholinergic drugs at nicotinic cholinergic receptors is little / nil as compared at muscarinic receptors.

- Anticholinergic drugs are considered – **selectively antimuscarinic.**

NATURALLY OCCURRING (TERTIARY AMINE)

Atropine

Scopolamine
(Alkaloids of belladonna plants

Synthetic compound
(Glycopyrrolate)
(Quaternery Ammoniums Derivatives)

- More potent than parent compounds
- Lack CNS activity because of poor penetration in brain

CLASSIFICATION

Natural alkaloid – Atropine, Scopolamine (hyoscine)

Semi-synthetic derivative – Homatropine, Atropine mithonitrate, Ipratropium bromide.

Synthetic compound –

a) Mydriatics : Cyclopentolate, tropicamide

b)Anti-seceretory –

- Quarternary : **Glycopyrolate**, Propantheline, Isopropamide
- Tertiary amines : Pirenzepine, Dicyclomine

c)Vasicoselective : Oxybutynin, flavoxate.

d)Anti-parkinsonian : Benzhexol, biperiden.

GLYCOPYROLATE

Glycopyrolate is a synthetic product that differs from atropine in being a quaternary amine.

The pre-medication dose is 0.005 – 0.01 mg/kg upto 0.2-0.3 mg in adults.

Clinical consideration :

- Because of its quaternary structure, glycopyrrolate can't cross BBB & is almost devoid of CNS & Ophthalmic activity.
- Potent inhibition of salivary gland & respiratory tract secretions is the primary rationale for using glycopyrrolate as pre-medication.
- Heart rate increases after IV administration.
- It has longer duration of action than atropine sulphate i.e. 2-4 hrs.

Differences

	Atropine	Glycopyrrolate
1. Lipid solubility	- Lipid soluble	- Poorly soluble (Quaternary ammonium compound)
2. Blood brain barrier crossing	- Good	- Minimum ability of crossing BBB
3. Metabolization	- 50% from liver	-
4. Excretion	- 18% unchanged	- 80% unchanged
5. Treatment	• bradycardia at low dose - 0.2 – 0.4 mg IV • Dose for intra operative bradycardia 1.2 mg -Max dose for bradycardia 3 mg Hiccups (Occurring after laryngeal mask placement) - 0.5 mg IV	Intra operative bradycardia
6. Heart rate	Increases	Increases

Differences

	Atropine	Glycopyrrolate
7. Effect on smooth muscles	Decreases tone of smooth muscles of biliary tract & ureter	
8. Antisialagauge effect	- Less then scopolamine	More
9. T½	- 2.3 hrs	Prolonged in uremic patients 1.25 hrs

COMPARATIVE EFFECTS OF ANTICHOLINERGIC DRUGS

	Sedation	Antisialagogue	Increase Heart Rate	Relax smooth Muscles
Atropine	+	+	+++	++
Scopolamine	+++	+++	+	+
Glycopyrrolate	0	++	++	++

	Mydriasis cycloplegia	Prevent Motion induced Nausea	Decrease Gastric Hydrogen Ion secretion	Alter Fetal Heart Rates
Atropine	+	+	+	0
Scopolamine	+++	+++	+	?
Glycopyrrolate	0	0	+	0

GLYCOPYRROLATE

CENTRAL ANTICHOLINERGIC SYNDROME

Anticholinergic drugs like scopolamine, atropine can enter central nervous system (CNS) and produce some unusual symptoms which are characterized in a syndrome which is known as central anticholinergic syndrome.

Symptoms are -

- Restlessness
- Hallucination to somnolence
- Unconsciousness

Glycopyrrolate does not easily cross BBB & not likely cause CACS.

MECHANISM OF ACTION

Anticholinergic are the class of drugs that **block the neurotransmitter acetylcholine in CNS and PNS.**

Anticholinergic drugs **combine reversibly with muscarinic cholinergic receptors thus preventing access of neurotransmitter acetylcholine in these sites.**

MECHANISM OF ACTION

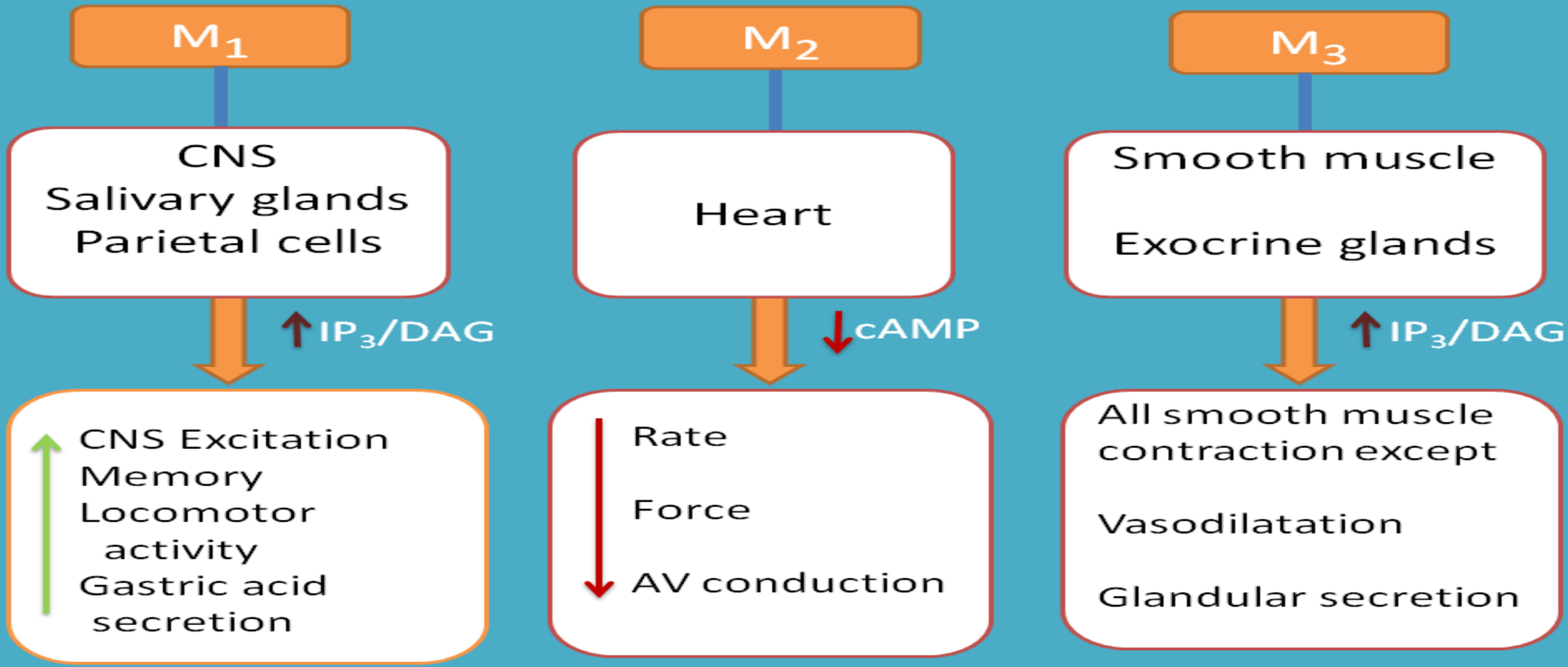
Glycopyrrolate competitively blocks acetylcholine, at muscarinic receptors M1, M2, & M3

Resulting in Parasympatholytic effect and allows for dominant Sympathetic activity.

It does not cross the BBB, (unlike Atropine) therefore does not exert CNS effects .

Muscarinic acetylcholine receptors

Muscarinic receptors are classified from M1 to M5.



M4 and M5 are mainly present within the CNS and their exact role still unknown

INDICATION

It is an anticholinergic indicated: in anesthesia (adult and pediatric patients)

- For reduction of airway or gastric secretions, and volume and acidity of gastric secretions, and blockade of cardiac inhibitory reflexes during induction of anesthesia and intubation,
- Intraoperatively to counteract surgically or drug-induced or vagal reflex associated arrhythmias, and
- For protection against peripheral muscarinic effects of cholinergic agents.

DOSAGE AND ADMINISTRATION-ADULTS

Glycopyrrolate may be administered intramuscularly (IM), or intravenously (IV), with or without dilution, in the following indications:

- Preanesthetic Medication: 0.004 mg/kg IM, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia Intraoperative

- Medication: single doses of 0.1 mg IV and repeated, as needed, at intervals of 2 to 3 minutes

- Reversal of Neuromuscular Blockade: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine Peptic Ulcer: 0.1 mg IV or IM at 4-hour intervals, 3 or 4 times daily

DOSAGE AND ADMINISTRATION- PEDIATRIC

Preanesthetic Medication: 0.004 mg/kg IM, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia. Patients under 2 years of age may require up to 0.009 mg/kg Intraoperative

Medication: 0.004 mg/kg IV, not to exceed 0.1 mg in a single dose and repeated, as needed, at intervals of 2 to 3 minutes

Reversal of Neuromuscular Blockade: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine Peptic Ulcer: GLYRX-PF is not indicated for the treatment of peptic ulcer in pediatric patients

METABOLISM

- ✓Undergoes little metabolism
- ✓80% excreted unchanged via kidney and liver.

USE WITH CAUTION

- In hepatic and renal disease
- Ulcerative colitis
- Asthma
- Glaucoma
- Urinary Retention

SIDE EFFECTS

Atropine Like Side effects

- Reduces the body's sweating ability
- It can cause fever, flushing and heat stroke in hot environment.
- Tachycardia
- Dry Mouth……40% & Difficulty in urinating
- Headaches & Constipation
- It induces drowsiness or blurred vision an effect exacerbated by the consumption of alcohol.

Neostigmine and Glycopyrrolate

Neuromuscular blocking agent (NMBA)

- To **aid stable mechanical ventilation** by **blocking spontaneous respiratory movements or, more frequently, to provide more suitable conditions for surgery**.

- Neuromuscular blocking drugs **do not produce sedation, hypnosis, or analgesia**.

Laboratory Animal Anaesthesia 4th Edition 2016; 109-140

Why reversal for NMBA is required?

Residual neuromuscular blockade

- Residual paralysis following extubation of the trachea, unfortunately, is still common.
- It should be reversed to prevent:

✓

✓

✓

✓ CO_2 retention (failure to remove excess CO_2)

✓

Residual neuromuscular block should no longer be tolerated in the recovery room, even if it is not severe enough for the patient to require re-intubation.

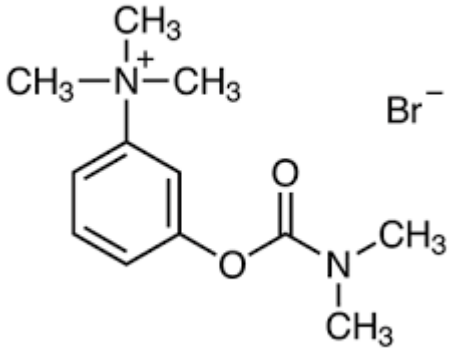
Residual block is associated with excess morbidity and is quite uncomfortabl patients.

Require re-intubation in the recovery room.

A residual neuromuscular block should therefore always be reversed.

J Biomed Res. 2019 Jul; 33(4): 217–220.

Reversal agent for NMBA (Neostigmine)



Cholinesterase Inhibitors

Neostigmine is water-soluble, an ionized compound that reversibly inhibits the enzyme acetylcholinesterase.

Its FDA indication is for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery.

Limitations of neostigmine

- Neostigmine produces muscarinic reactions (mimicking acetylcholine actions), such as **slowing heart rate, increased airway secretions and**

Therefore, it is necessary to use the anticholinergic drug (atropine, glycopyrrolate) to antagonize the side effects of neostigmine.

- In severe cases, slowing heart rate causes **hemodynamic instability and endangers the life of the patient.**

Am J Transl Res. 2021; 13(11): 12996–13002.

Advantages for administering anticholinergics (atropine, glycopyrrolate) in anaesthesia

- Antisialagogue effect (decrease the flow rate of saliva)
- Creating a sedative and amnesic effect (atropine)
- Prevents reflex bradycardia

Am J Transl Res. 2021; 13(11): 12996–13002.

Neostigmine

Glycopyrrolate

Rationale to use glycopyrrolate with neostigmine

Neostigmine + **Glycopyrrolate**

Bradycardia

Excessive secretions

Prevents bradycardia

Excessive secretions

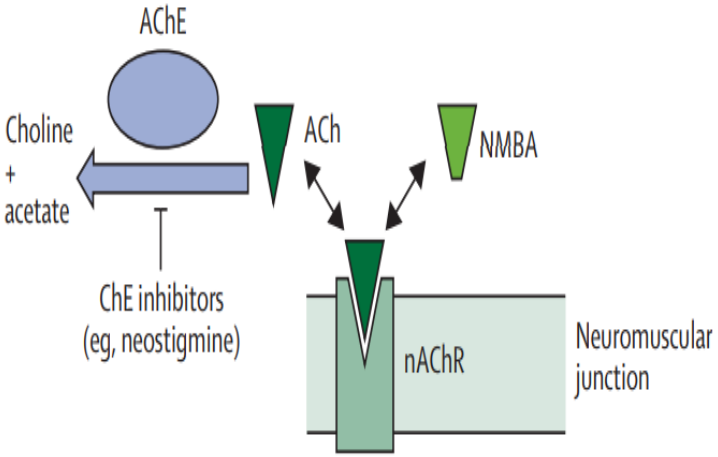
Am J Transl Res. 2021; 13(11): 12996–13002.

PRODUCT ATTRIBUTES

Introduction

Neostigmine

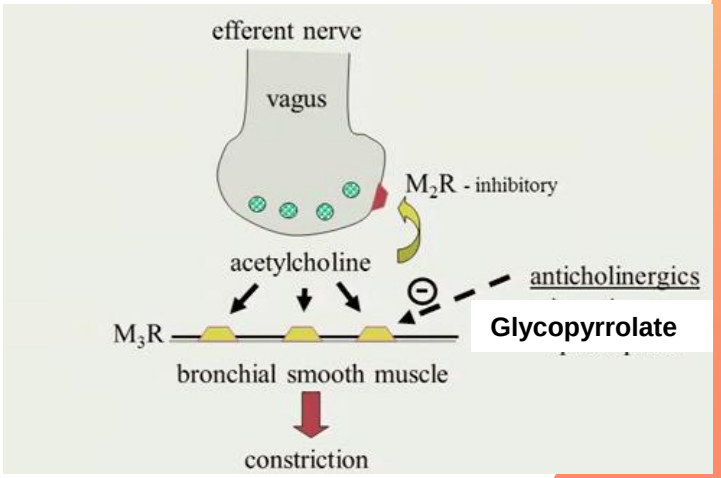
Cholinesterase Inhibitors



Inhibit ChE, protect ACh from hydrolysis

Glycopyrrolate

Anticholinergic Agent



Indication

- It is indicated in patients age two years and above for the reversal of the effects of NMBA (competitive) after surgery

Dosage and administration

Route of administration	Intravenous
Adults and Elderly	1-2 ml over a period of 10-30 seconds Neostigmine metisulfate- 2.5-5 mg Glycopyrrolate 0.5- 1 mg Alternatively 0.02ml/kg over a period of 10-30 seconds Neostigmine metisulfate- 0.05mg/kg Glycopyrrolate 0.01 mg/kg
Paediatric population	0.02ml/kg over a period of 10-30 seconds Neostigmine metisulfate- 0.05mg/kg Glycopyrrolate 0.01 mg/kg Alternatively Dilute to 10ml with WFI BP or NaCl injection BP 0.9% w/v and administer 1ml per 5kg body weight

Onset of action- 1 minute

- These doses may be repeated if adequate reversal of neuromuscular blockade is not achieved.
- Total doses in excess of 2ml are not recommended as this dose of neostigmine may produce depolarising neuromuscular block.

Side Effects

Most common adverse reactions to glycopyrrolate are related to anticholinergic pharmacology and may include

- Xerostomia (dry mouth)
- Blurred vision and photophobia due to mydriasis (dilation of the pupil)
- Tachycardia (increase in heart rate)

Most common adverse reactions to neostigmine during treatment:

- Bradycardia
- Nausea
- Vomiting Blurred vision
- Photophobia (sensitive to light)

Warning and Precaution

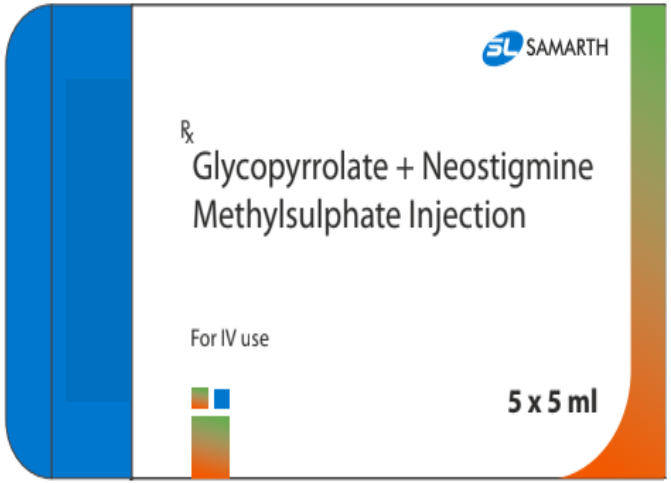
- Hypersensitivity
- Neuromuscular Dysfunction
- Cholinergic Crisis
- Precipitation of Acute Glaucoma
- Drowsiness and Blurred Vision

Special Population

Pregnancy	No data available. Risk to the fetus clearly outweighs any potential benefit to the mother
Lactation	The developmental and health benefits of breast feeding should be considered along with the mother's clinical need and any potential adverse effects on the breastfed child.
Pediatric Use	It is not recommended to be used in pediatric patients less than 2 years of age.
Geriatric Use	Dosage adjustments are not generally needed in geriatric patients; however, they should be monitored for longer periods than younger adults
Renal Impairment	No adjustments in dosage however, patient should be closely monitored.
Hepatic Impairment	No adjustments in dosage.

Contraindications

- Hypersensitivity.
- Patients with mechanical obstruction of the gastrointestinal or urinary tracts.
- Prolonged QT interval.



Composition:
Each 5 ml contains:
Glycopyrrolate IP 0.5 mg
Neostigmine Methylsulphate IP 2.5 mg
Water for Injections IP q.s.

Dosage: As directed by the Anaesthesiologist.

Store below 25°C., protected from light. Do not freeze.

Keep the medicine out of reach of children.

Discard unused solution after use.

Caution: Not to be sold by retail without the prescription of a Registered Medical Anaesthesiologist.

Mfg. Lic. No. : MB/09/791
Batch No. :
Mfg. Date :
Expiry Date :
M.R.P. ₹ (Incl. of all Taxes) :

Manufactured by:
SAMARTH LIFE SCIENCES PVT.LTD.
UNIT II: Plot No.2, Industrial Area, Lodhimajra, Baddi, Himachal Pradesh -173 205, India.
H.O.: Ram Mandir Road, Goregaon (W), Mumbai - 400 104, India.

™ Trade Mark under Registration

Clinical Evidences

Glycopyrolate vs. Atropine

Difference between Glycopyrolate and Atropine

	Atropine	Glycopyrolate
Sedation (Crosses BBB)	+	-
Antisialogogue (Anti- saliva secretion effect)	+	++
Tachycardia (Increase in heart rate)	+++	++
Smooth muscle relaxants	++	++
Ocular effect	+	-
Rate of action	Fast	Slow

Antisialgogue: Decreases the flow rate of saliva

Br. J. Anaesth. (1977), **49**, 825

GLYCOPYRROLATE–NEOSTIGMINE MIXTURE FOR ANTAGONISM OF NEUROMUSCULAR BLOCK: COMPARISON WITH ATROPINE–NEOSTIGMINE MIXTURE

R. K. MIRAKHUR, J. W. DUNDEE AND R. S. J. CLARKE

Study Protocol

Forty fit adult patients of both sexes were studied who were undergoing various intra-abdominal operations.

- Neostigmine 2.5 mg and atropine 1.2 mg (N=20)
- Neostigmine 2.5 mg and glycopyrrolate 0.5mg (N=20)

Atropine causes an initial tachycardia while the heart rate changed little with glycopyrrolate

Mean heart rate (±SEM) after injection of antagonizing mixture. (n=20)

Time after injection (min)	Atropine–neostigmine group	Glycopyrrolate–neostigmine group
Before injection	88.6 ±4.80	87.0 ±3.28
1	97.8 ±4.38	85.7 ±3.73
2	96.1 ±4.13	87.1 ±3.69
3	94.2 ±4.33	84.0 ±3.67
4	89.7 ±4.30	81.9 ±4.47
5	84.8 ±4.59	80.5 ±4.40
6	80 0 ±4.14	79.0 ±4.46
60	77.4 ±3.51	76.9 ±3.59

Glycopyrrolate causes a marked and significant reduction in salivary secretion than atropine

Secretions during antagonism

	Number of patients	
	Atropine–neostigmine	Glycopyrrolate–neostigmine
Minimal	5	12
Moderate	12	6
Excessive	3	2
Total	20	20

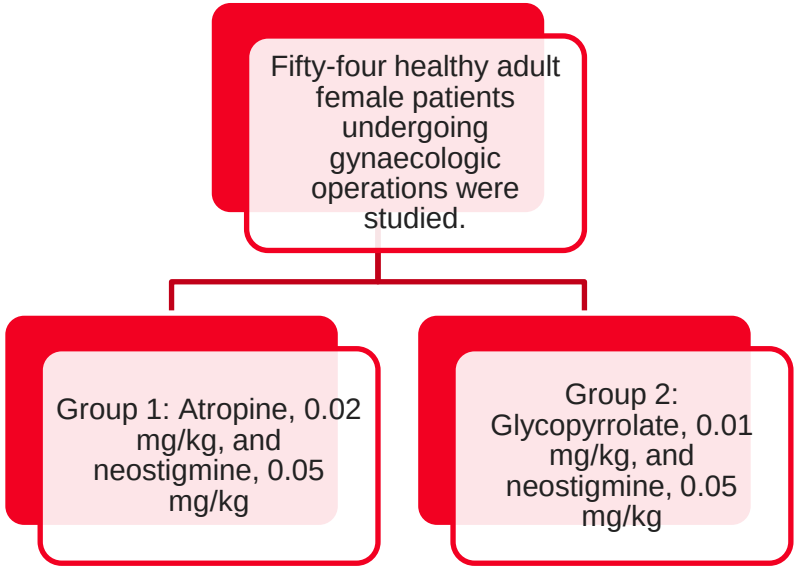
Conclusion

- Glycopyrrolate 0.2 mg to neostigmine 1.0 mg was found to be **safe and effective**.
- The **heart rates remained more stable with glycopyrrolate, and the frequency of arrhythmia,** which was both transient and of no consequence, was similar in the two groups.
- The **antisialogogue action of glycopyrrolate was superior** to that of atropine.

ANESTH ANALG
59:431–434, 1980

Glycopyrrolate–Neostigmine and Atropine–Neostigmine Mixtures Affect Postanesthetic Arousal Times Differently

Anis Baraka, MD,* Jean-Pierre Yared, MD,† Anne-Marie Karam, MD,‡ and Alon Winnie, MD§



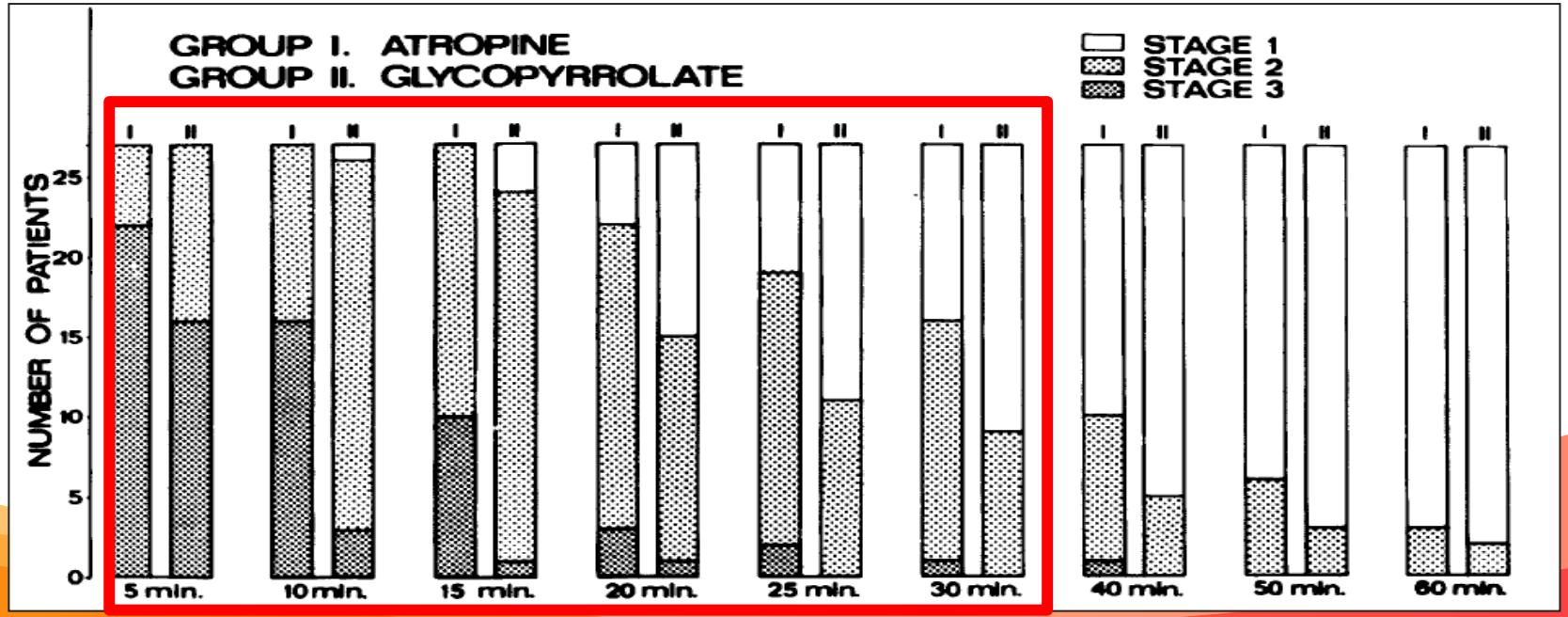
Primary end point: **Arousal time**

Anesthesia was induced in all patients with thiopental and was maintained with N20-02.

ANESTH ANALG 1980; 59: 431-434

Atropine-neostigmine significantly delayed arousal for the first 30 minutes following cessation of anesthesia and reversal of neuromuscular blockade.

Distribution of patients according to the arousal scores obtained at different intervals following reversal of neuromuscular blockade



ANESTH ANALG 1980; 59: 431-434

Conclusion

We conclude that the glycopyrrolate-neostigmine mixture is preferable to atropine-neostigmine for reversal of neuromuscular blockade. Both neostigmine and glycopyrrolate are quaternary ammonium compounds that do not cross the blood-brain barrier, and hence the peripheral muscarinic side effects of neostigmine can be adequately[4, 5] and selectively coun-

2021

Am J Transl Res 2021;13(11):12996-13002
www.ajtr.org /ISSN:1943-8141/AJTR0132945

Original Article

Glycopyrrolate versus atropine for preventing bradycardia induced by neostigmine injection after general anesthesia surgery: a randomized open, parallel-controlled multicenter clinical trial

group's heart rate remained at the baseline level for longer than the control group ($P<005$). There was no significant difference in the incidence of adverse reactions between the two groups of patients ($P>005$). Conclusion: Glycopyrrolate and atropine are safe to prevent heart rate slowing induced by the non-depolarizing muscle relaxant antagonist neostigmine, and glycopyrrolate is more conducive to maintaining a stable heart rate in patients.

2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade

Stephan R. Thilen, M.D., M.S. (co-chair),
Wade A. Weigel, M.D. (co-chair), Michael M. Todd, M.D.,
Richard P. Dutton, M.D., M.B.A., Cynthia A. Lien, M.D.,
Stuart A. Grant, M.D.,

Guideline Recommendation

Recommendation

- We **suggest neostigmine as a reasonable alternative to sugammadex at minimal depth of neuromuscular blockade**.
- To **avoid residual neuromuscular blockade when atracurium or cisatracurium** are administered and qualitative assessment is used, we **suggest antagonism with neostigmine at minimal neuromuscular blockade depth**. In the absence of quantitative monitoring, at least 10 min should elapse from antagonism to extubation. When quantitative monitoring is utilized, extubation can be done as soon as a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation.

Neuromuscular blocking agent is used to aid mechanical ventilation

Risk of residual neuromuscular blockade (Complications after anesthesia)

Cholinesterase inhibitors or reversal agent used (Neostigmine)

Neostigmine causes slowing of heart rate and increased airway secretions

Addition of anticholinergic drug (glycopyrrolate) antagonizes the side effects of neostigmine to prevent neostigmine induced bradycardia, hence the combination

Thank You

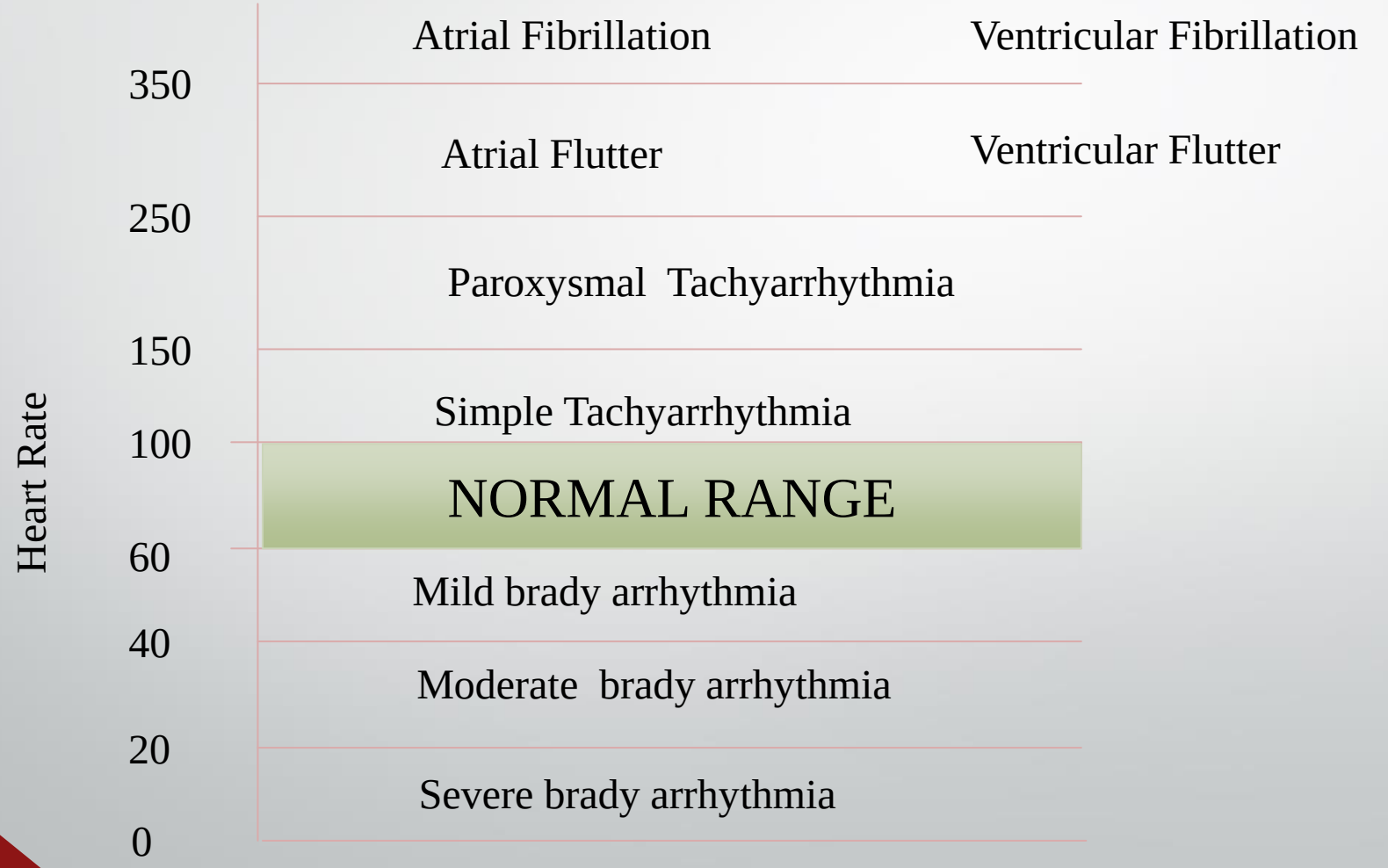
The Cardiovascular System

Basics

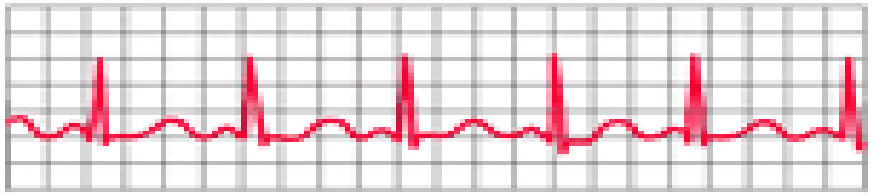
What is arrhythmia?

- An arrhythmia is a problem with the **rate or rhythm** of your heartbeat.

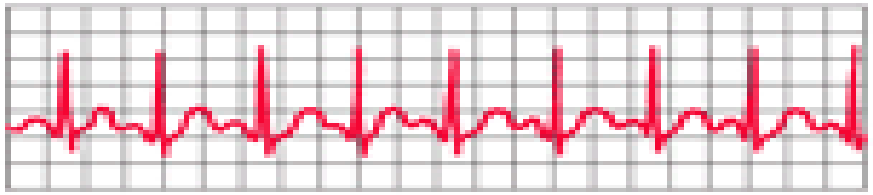
Classification – depending on HR



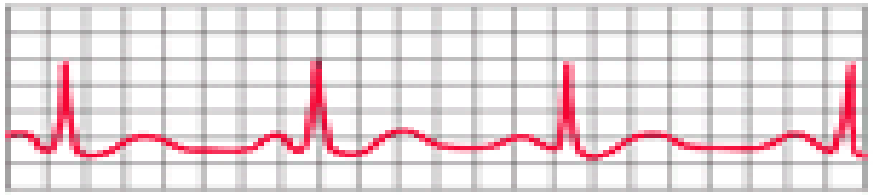
Normal Heartbeat



Fast Heartbeat



Slow Heartbeat

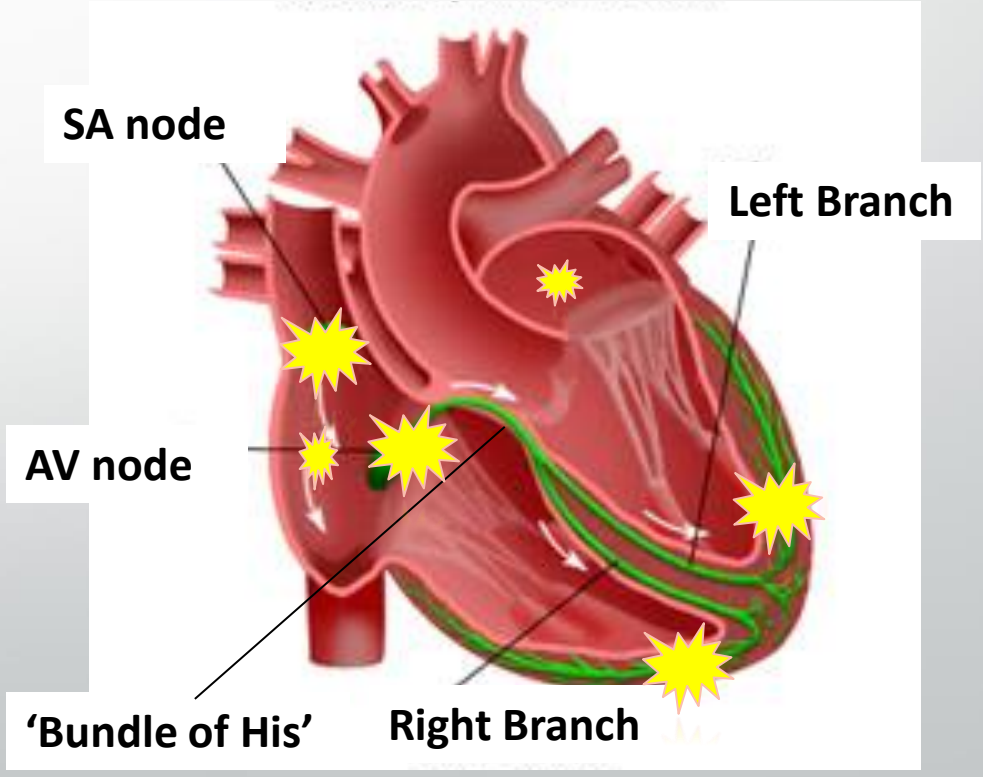


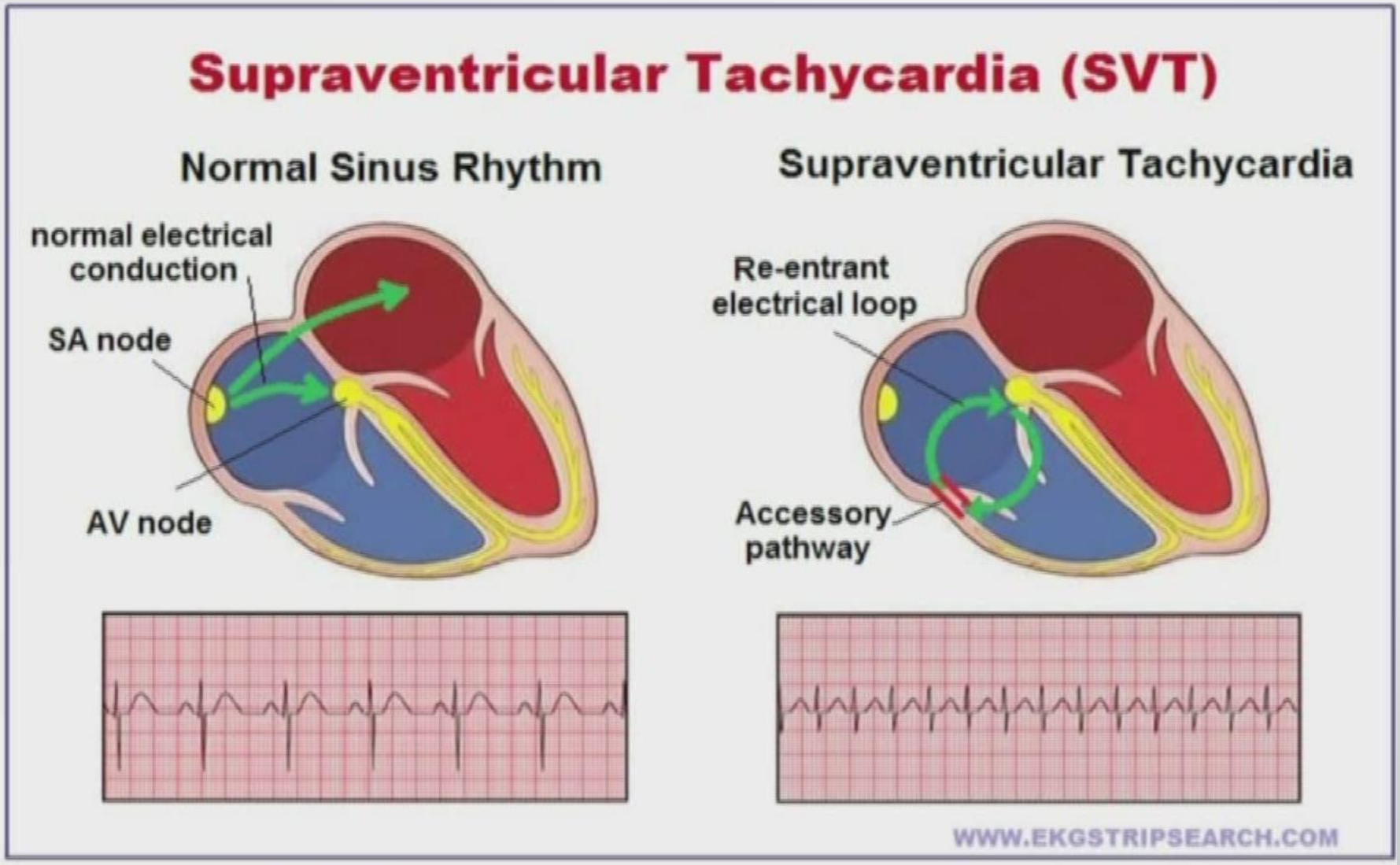
Focus of Arrhythmia

- Arrhythmias can arise from problems in the

Supraventricular Arrhythmias

- Sinus Arrhythmias
- Atrial arrhythmias
- Junctional /nodal arrhythmias
- Ventricular arrhythmias



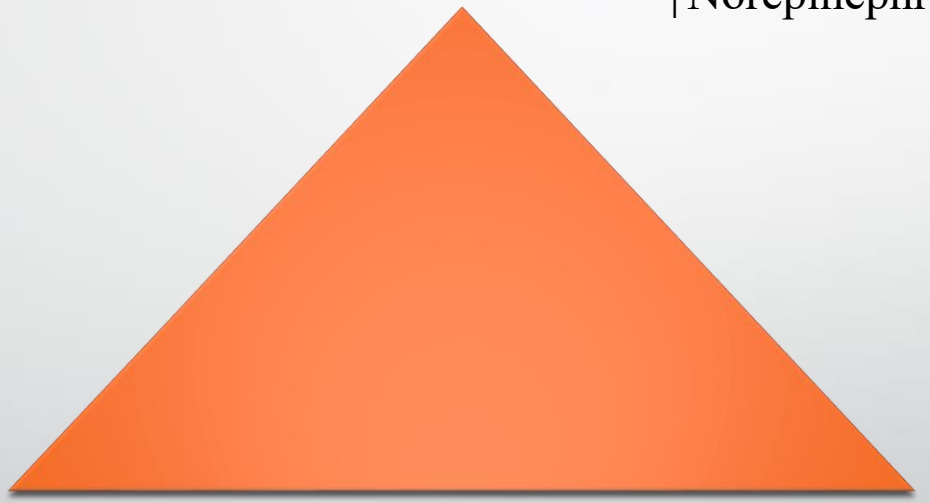

Supraventricular Tachycardia (SVT)
Normal Sinus Rhythm
Supraventricular Tachycardia
normal electrical conduction
SA node
AV node
Re-entrant electrical loop
Accessory pathway
WWW.EKGSTRIPSEARCH.COM

Causes of Arrhythmias

Automaticity → property of cardiac cells to generate spontaneous action potentials.

↑ **Automaticity** (undergo depolarization spontaneously)

↑Norepinephrine



Triggered Automaticity

Myocardial Ischemia
Myocardial Injury

Re-entry

Ischemic Focus (scar tissue)

Sinus node arrhythmias

- Two main types of Arrhythmias
  - Sinus Bradycardia: Heart rate is too slow (< 60 beats/min)
  - Sinus Tachycardia: Heart rate is too fast (> 100 beats/min)

Atrial Origin

- Atrial Flutter

  Impulse generated from single ectopic site

  ATRIAL RATE = 250 – 350 beats/ min

  VENTRICULAR RATE: 80-120 beats/min

- Atrial Fibrillation

  Impulse is generated from many ectopic sites

  ATRIAL RATE = >350 beats/ min

  VENTRICULAR RATE: 60-100 beats/min

Ventricular Origin (more dangerous)

- Ventricular Tachycardia

  Single strong ectopic site

  Leads to ventricular premature beats (100-250 beats /min)

- Ventricular Fibrillation

  Multiple weak ectopic sites

  Incomplete contraction

  Heart pumps little or no blood

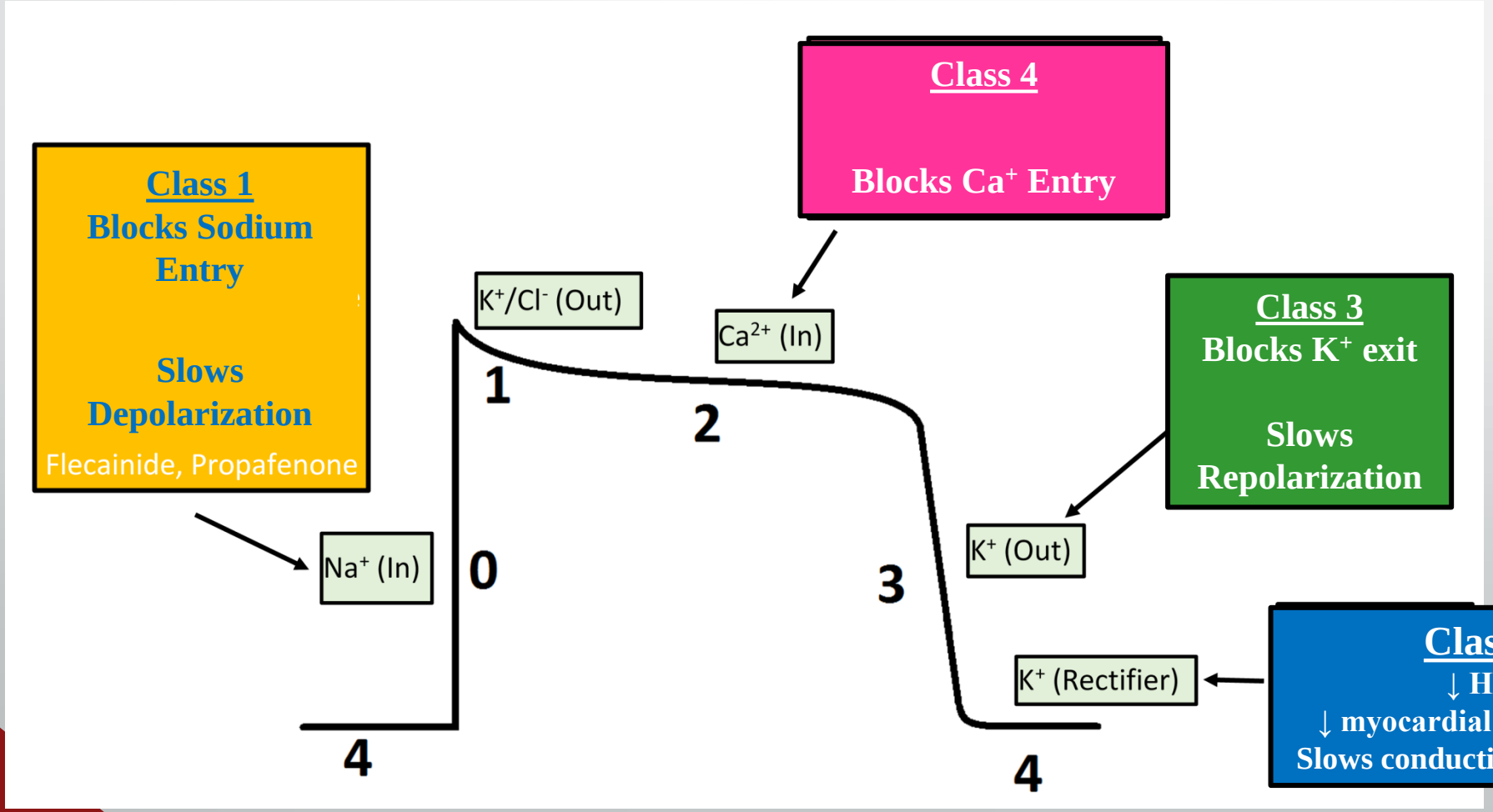
  Can lead to cardiac arrest

Symptoms of Arrhythmia

- Fast or slow heart beat
- Palpitations
- Skipping beats
- Light-headedness or dizziness
- Chest pain
- Shortness of breath
- Sweating

Antiarrhythmic drugs

Drugs that affect conduction of electrical impulse within the heart



Antiarrhythmic drugs

Antiarrhythmic drugs

Class	Actions	Drugs
I.	*Membrane stabilizing agents (Na⁺ channel blockers)*	
	A. *Moderately decrease dv/dt of 0 phase*	Quinidine, Procainamide Disopyramide, Moricizine
	B. *Little decrease in dv/dt of 0 phase*	Lidocaine, Mexiletine
	C. *Marked decrease in dv/dt of 0 phase*	Propafenone, Flecainide
II.	*Antiadrenergic agents (β blockers)*	Propranolol, Esmolol Sotalol (also class III)
III.	*Agents widening AP (prolong repolarization and ERP)*	Amiodarone, Bretylium (also class II) Dofetilide, Ibutilide
IV.	*Calcium channel blockers*	Verapamil, Diltiazem

Note: Class IA agents also have Class III property; Propranolol has Class I action as well; sotalol and bretylium have both Class II and Class III actions.

In addition

1. *For PSVT* : Adenosine, Digitalis.
2. *For A-V block* : Sympathomimetics—Isoprenaline, etc. Anticholinergics—Atropine.
3. Digitalis is used in AF, AFl and PSVT to control ventricular rate.

K D Tripathi 6th Edn pg 511

ESOCARD

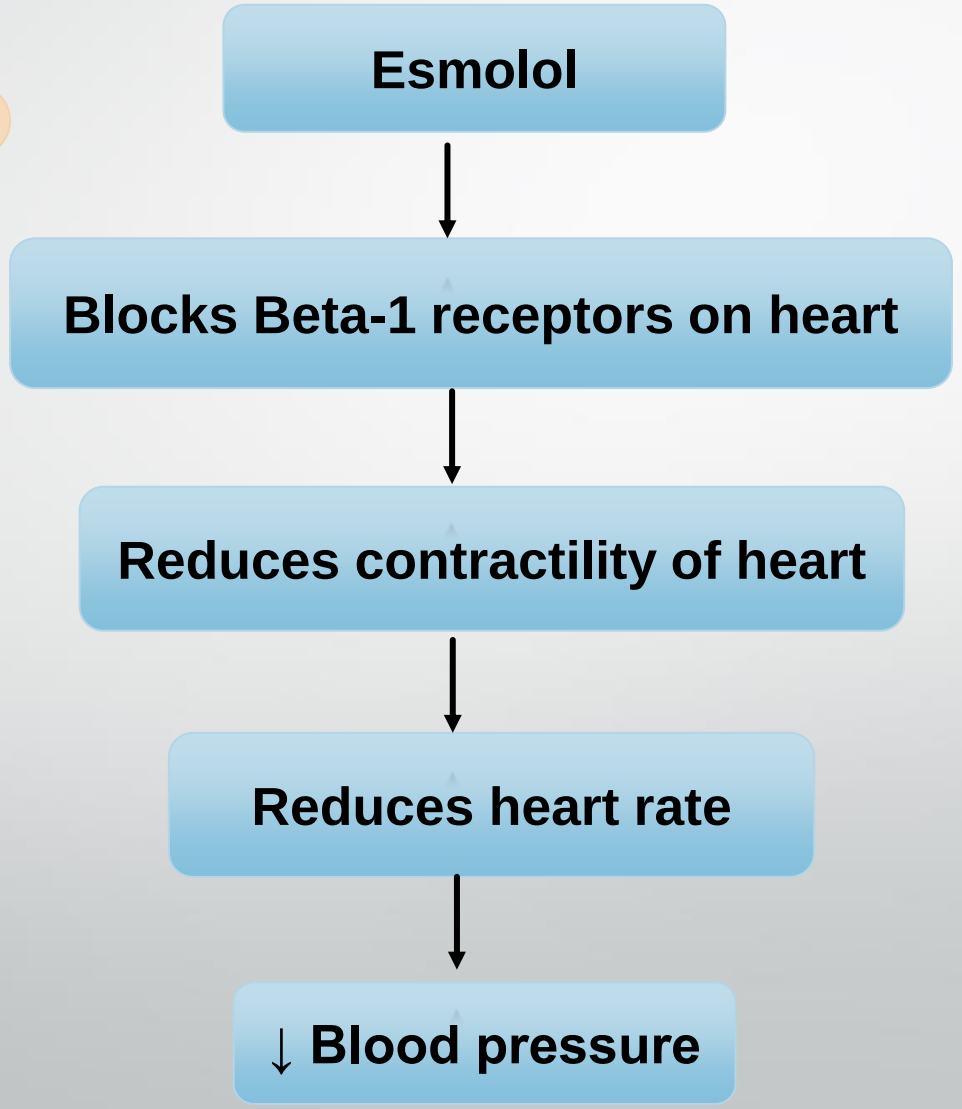
Inj Esmolol 100mg/10 ml

Introduction

- Cardio-selective short acting beta blocker

Mechanism of Action

Has a rapid onset and a very short duration of action by which the dose can be quickly adjusted



Indication

- Hypertension occurring in the perioperative phase
- Supraventricular tachycardia, in perioperative, postoperative period
- It is not indicated for use in children aged up to 18 years

Dosage for Hypertension

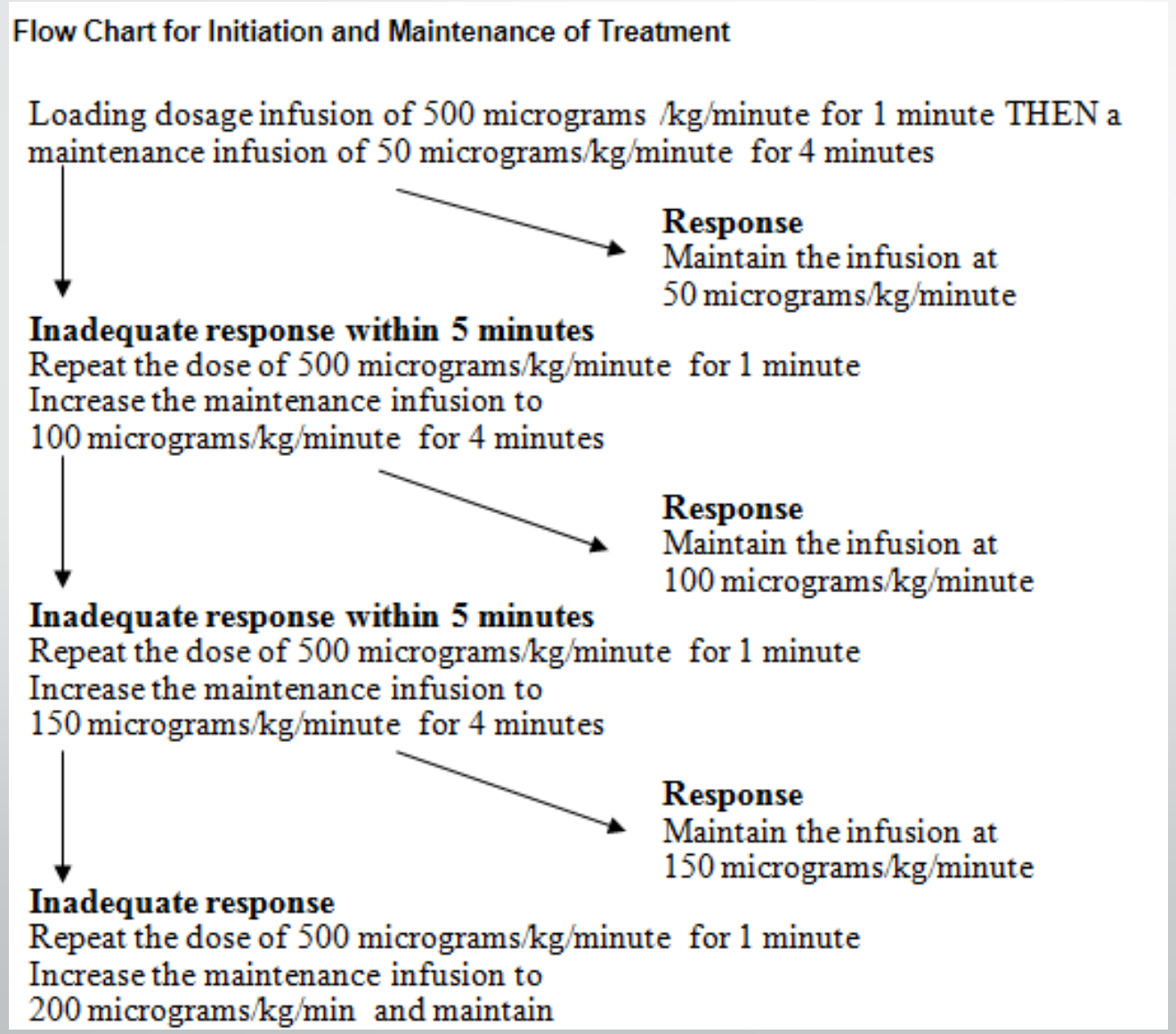
- **Immediate Control**
- Administer 1 mg/kg as a bolus dose over 30 seconds followed by an infusion of 150 mcg/kg/min if necessary.

- **Gradual Control**
- Administer 500 mcg/kg as a bolus dose over 1 minute followed by a maintenance infusion of 50 mcg/kg/min for 4 minutes.

- **Maximum Recommended dose**
- 250-300 mcg/kg/ min

US PI

Dosage for arrhythmia



SPECIAL POPULATION

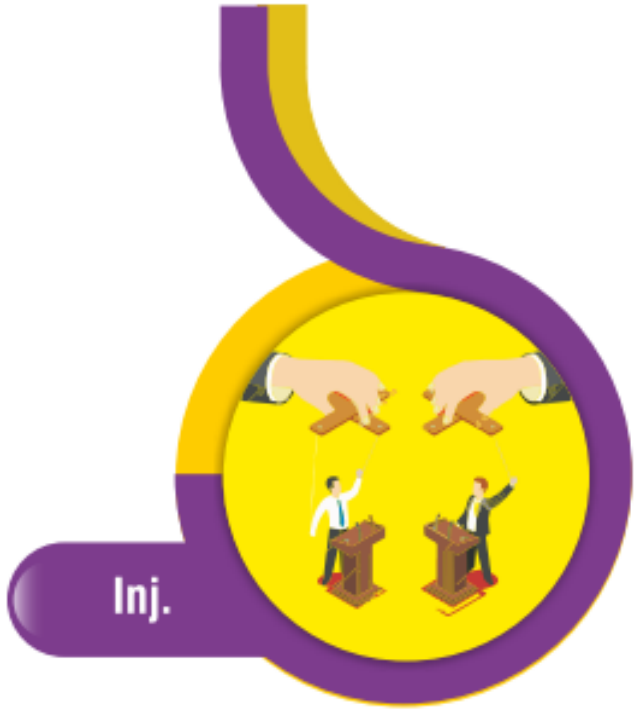
Patient population	
Pregnancy	To be given if potential benefit outweighs the risk
Elderly	Start with a lower dosage and monitor the patient
Renal Impairment	Caution needed when administering Esmolol hydrochloride via infusion.
Liver Impairment	No special precautions required.
Paediatric	Not indicated for use in children aged up to 18 years

ESO

For rapid & precise control of heart rate & BP

℞ ESOCARD

Inj. Esmolol HCl 100mg/10ml



The Ultra Short Acting Cardioselective β_1 Blocker

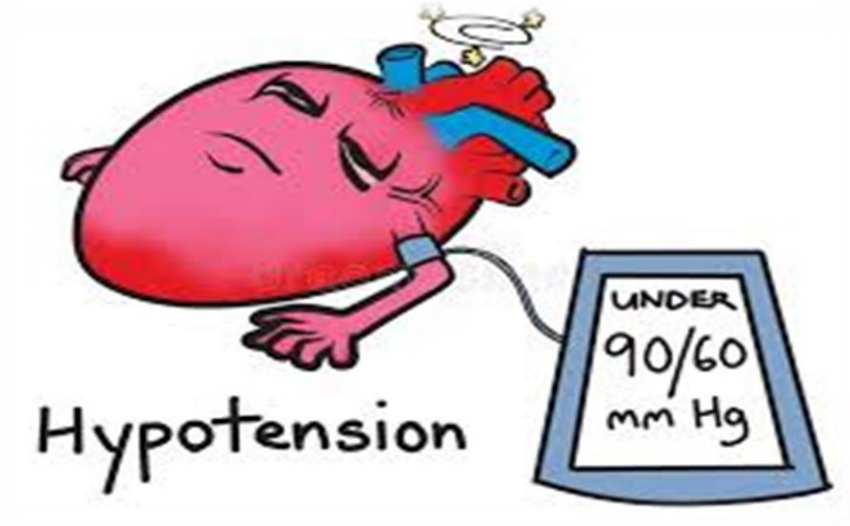
- Ideal drug for preventing acute increases in HR & SAP[1]
- Maintains better myocardial oxygen delivery[2]
- Positive effect on the cardiac recovery in CPB surgeries[2]

HYPOTENSION

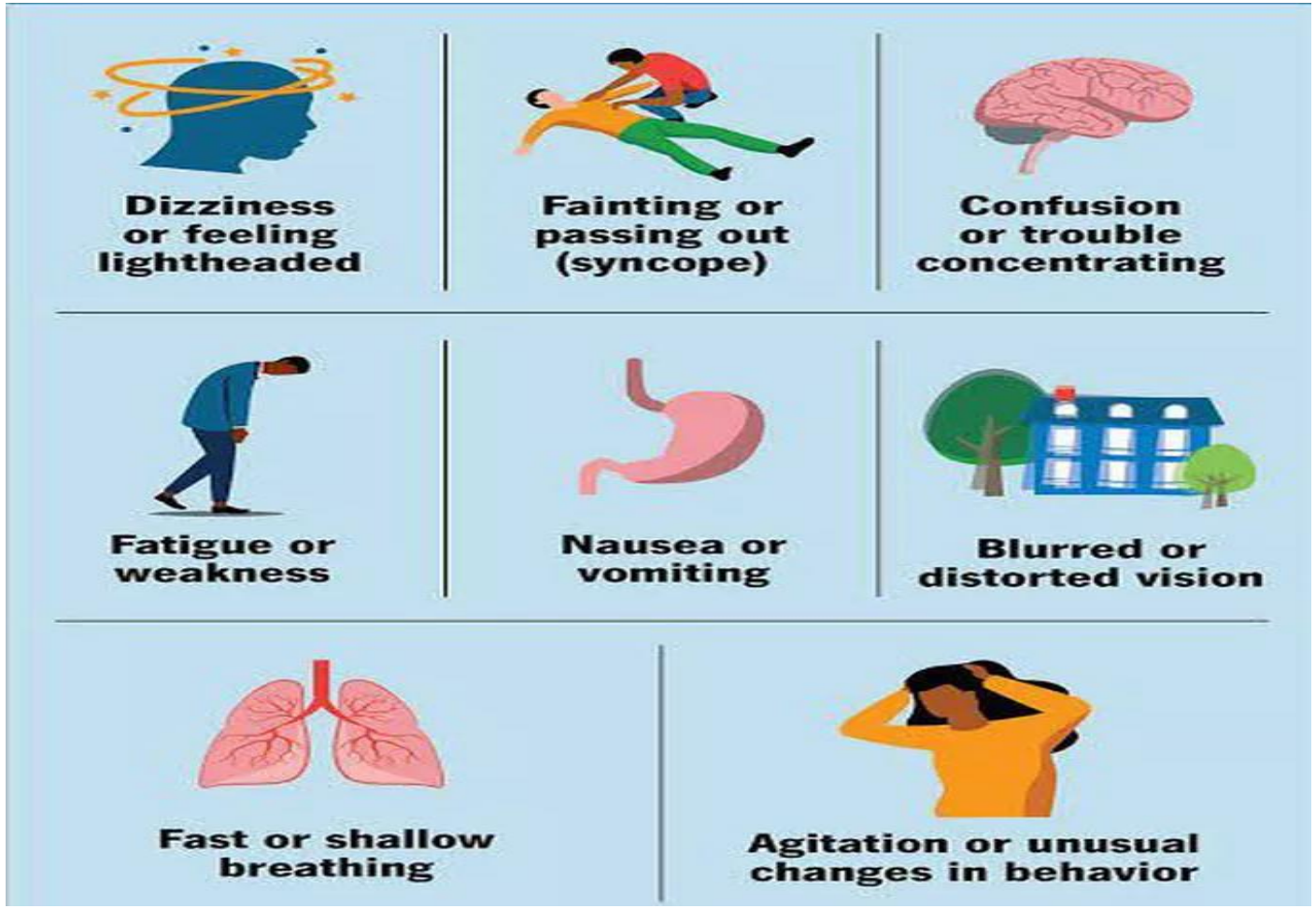
WHAT IS HYPOTENSION?

Hypotension, or **low blood pressure**, is a condition in which the force of blood against the walls of the arteries is lower than normal.

Low blood pressure is a reading below 90/60 mm Hg.



SIGNS AND SYMPTOMS



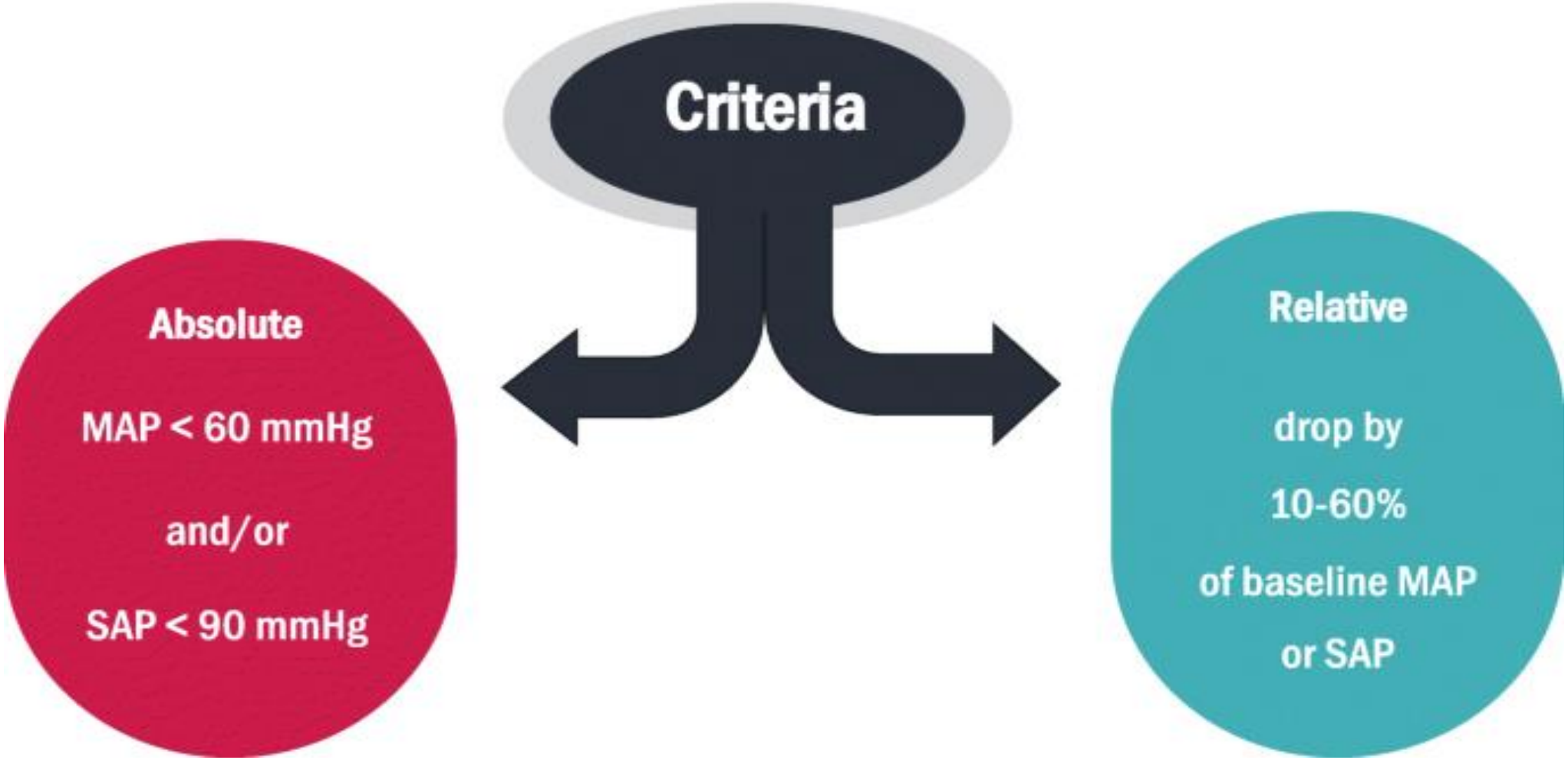
ANAESTHESIA AND HYPOTENSION

- **General anaesthesia** commonly results in **mild hypotension** due to the effects of **intravenous induction agents and inhalational agents in reducing cardiac output and systemic vascular resistance.** In the elderly induction agents need to be given slowly and at reduced doses to avoid severe hypotension.

- **Spinal and epidural anaesthesia cause vasodilatation due to sympathetic block**, and if the block is above T4 may also result in decreased myocardial contractility and bradycardia.

- Patients undergoing combined **regional and general anaesthesia are particularly susceptible to hypotension.**

Perioperative Hypotension



CAUSES OF HYPOTENSION

- **Deceased Cardiac Output:** Cardiac output (CO) is the amount of blood pumped by the heart/ minute and is the mechanism whereby blood flows around the body, especially providing blood flow to the brain and other vital organs.

- **Decreased Venous Return (Preload):** Preload is the end diastolic pressure of the heart when the ventricle has become filled with blood.

- **Arterial Vasodilation (Afterload):** The afterload is the amount of pressure that the heart needs to exert to eject the blood during ventricular contraction.

TREATMENT OF HYPOTENSION

Hypotension

= decrease in MAP 20-30% below baseline

Initial checklist

- ✓ Verify BP (e.g. surgeon leaning on cuff?)
- ✓ Check other vital signs (heart rate, CO_2, oxygenation)
- ✓ Inform surgeon (ask about blood loss / venous compression)

Initial treatment

- iv wide open (crystalloids)
- Decrease or stop anæsthetic
- Increase FiO_2
- Administer inotropes / vasopressors? (ephedrine / phenylephrine / epinephrine / vasopressin)
- Consider:
  - Head down position
  - More / larger iv access
  - Give colloids / blood ?

FRENIN

Phenylephrine HCL Inj. 10mg/ml

INTRODUCTION

- Phenylephrine is a vasoconstrictor drug

INDICATION

- Treatment of hypotension during spinal, epidural and general anaesthesia.

- Prolongation of anesthesia

MECHANISM OF ACTION

For hypotension during anaesthesia

- Phenylephrine is a potent vasoconstrictor that acts almost exclusively by stimulation of alpha-1-adrenergic receptors.
- Arterial and Venous vasoconstriction will increase blood pressure

Prolongation of anaesthesia

- Phenylephrine decrease neural blood flow and this delays the absorption of the anesthetics, which prolongs the duration of their effects. (Korean J Anesthesiol. 2011 Nov; 61(5): 372–376.)

PHARMACOKINETICS

Bioavailability	38% through GI tract
Protein binding	95%
Metabolism	Hepatic (monoamine oxidase)
Biological half-life	2.1–3.4 h
Duration	20 mins

DOSAGE

Intravenous bolus injection:

- 50 to 100 mcg/kg, which can be repeated until the desired effect is attained. Do not exceed 100 mcg/kg

Continuous infusion:

- Initial dose is 25 to 50 micrograms/min.
- The doses may be increased or decreased to maintain the systolic blood pressure close to the normal value.

https://www.medicines.org.uk/emc/product/2065

DOSAGE

Indication	Dosage
Mild to moderate hypotension	SC or IM: 2 to 5mg,initial dose should not exceed 5mg IV: 0.1 to0.5 mg, initial dose should not exceed 0.5mg
Severe hypotension and shock	Continuous infusion: add 10mg in 500ml dextrose inj. & start the infusion at about 100-180mcg/min.. maintenance dose 40-60 mcg/min
Spinal anesthesia-hypotension	IV: Initial dose should not exceed 0.2mg. Subsequent dose 0.1 to 0.2 mg
Prolongation of spinal anesthesia	2 to 5 mg of FRENIN to anesthetic solution
Vasoconstrictor for regional anesthesia	1 mg of FRENIN to every 20ml of local anesthetic solution
Paroxysmal supraventricular tachycardia	Initial dose should not exceed 0.5 mg & preceding dose not more than 0.1 to 0.2mg

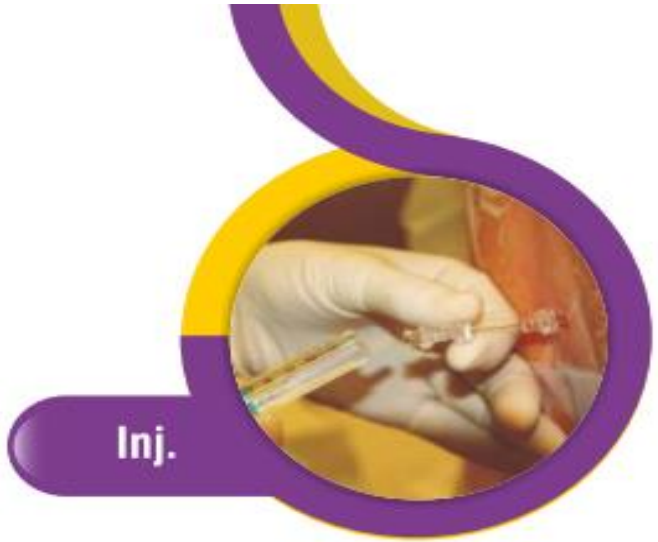
To prolong anesthesia & prevent spinal anesthesia induced hypotension

℞

FRENIN

Inj. Phenylephrine HCl 10mg/ml

PRESERVATIVE FREE



An **Anesthetic** Vasopressor

FRE

- Better venoconstriction & reduces the decrease in cardiac preload[1]
- Highly potent than ephedrine[1]
- Less frequent fetal acidosis in cesarean section[2]

Available with a **Free Syringe**

1. British Journal of Anaesthesia 2006; 96 (1): 95–9