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Printed in the United States of America

Print number: 0 9 8 7 6 5 4 3 2

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CHAPTER 1 - EMBRYOLOGY OF HEART

- The heart develops from splanchnic mesoderm in the later half of 3rd week and starts beating by the 4th week of gestation. Neural crest cell migration plays a significant role in the development of the heart.

- Single heart tube is formed by the fusion of primordial heart tubes (cardiogenic cells). Heart tube will undergo dextral looping (bend to right), rotation, and other changes that will give rise to various embryological dilations such as truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium and sinus venosus.

![Figure 1.1: sequence of events in embryological development of the heart](image)

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<tr>
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<th>ADULT DERIVATIVE</th>
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<tr>
<td>Truncus arteriosus</td>
<td>Ascending aorta, pulmonary trunk, semilunar valves</td>
</tr>
<tr>
<td>Bulbus cordis</td>
<td>Smooth part of left ventricle (aortic vestibule) and right ventricles (conus arteriosus)</td>
</tr>
<tr>
<td>Primitive atria</td>
<td>Trabeculated part of atria</td>
</tr>
<tr>
<td>Primitive ventricles</td>
<td>Trabeculated part of ventricles</td>
</tr>
<tr>
<td>Left horn of sinus venosus</td>
<td>Coronary sinus</td>
</tr>
<tr>
<td>Right horn of sinus venosus</td>
<td>Smooth part of right atrium</td>
</tr>
</tbody>
</table>
THUNDERNOTE: KARTAGENER SYNDROME

Pathogenesis: Defect in dynein arms.

Dynein arms primarily mediate cardiac looping. A defect in these arms will not allow the heart to shift toward the left side and therefore, right-sided heart (dextrocardia) is seen in this pathology.

Clinical presentation: Bronchiectasis, chronic sinusitis and situs inversus (in about 50% case only)

Most common infectious organisms: Staphylococcus aureus, Hemophilus influenza, Streptococcus pneumonia

Management: Routine follow-up, treat symptomatically (no guidelines exist due to lack of data)
CHAPTER 2 - ANATOMY

MEDIASTINUM

The mediastinum is central, midline thoracic cavity, which is surrounded anteriorly by the sternum, posteriorly by 12 thoracic vertebrae and laterally by pleural cavity.

The mediastinum is divided into the superior mediastinum and inferior mediastinum.

1) Superior mediastinum

- The superior mediastinum is a cavity that is above the plane of sternal angle (above 2nd rib).

- It contains superior vena cava, aortic arch and its branches, trachea, esophagus, thoracic duct, vagus, and phrenic nerve.

2) Inferior mediastinum

- The inferior mediastinum is a cavity that is located below the plane of the sternal angle. It is further divided into three parts - anterior, middle and posterior mediastinum.

The anterior mediastinum is anterior to the heart and contains remnants of the thymus.

The middle mediastinum contains the heart and great vessels.

The posterior mediastinum contains everything that is below the posterior margin of heart i.e. thoracic aorta, esophagus, thoracic duct, azygos veins, and vagus nerve.

Widened mediastinum is when the diameter is greater than 6 cm on upright chest x-ray or greater than 8cm on supine chest x-ray. Few causes of widened mediastinum are:

- Aortic dissection
- Dorsal spinal vertebral fracture (T4-T8)
- Infections with bacillus anthracis (anthrax)
- Aortic aneurysm

Figure 2.1: Chest x-ray, 1: widened mediastinum, 2: aortic knob*
• Esophageal rupture can present with air in the mediastinum leading to palpable crepitus on the anterior chest wall.

• Most posterior part of the heart is left atrium. The esophagus is located just behind the left atrium. Enlargement of left atrium due to any reasons (most common cause is mitral stenosis) will compress the esophagus, and lead to dysphagia.

• Left atrial enlargement and aortic aneurysm can also cause hoarseness of voice due to compression of the left recurrent laryngeal nerve, which loops around ligamentum arteriosus/arch of the aorta.

• Left vagus nerve branch loops around arch of aorta (right vagus nerve loops around right subclavian artery)

MOST COMMON PATHOLOGY IN MEDIASTINUM

• Most common pathology in anterior mediastinum: thymoma

• Most common pathology in middle mediastinum: congenital cysts

• Most common pathology in posterior mediastinum: neurogenic tumors

• Overall most common pathology in mediastinum: neurogenic tumors
Figure 2.2: CT at T4*

Figure 2.3: CT at T5*
SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome is a group of symptoms that occurs due to external compression of superior vena cava. It is characterized by:

- Shortness of breath
- Facial swelling
- Upper limb edema
- Headache
- Venous distension in head and neck
- Retinal hemorrhage and stroke can also be present

It is a medical emergency because it can raise intracranial pressure and increases risk of aneurysm/rupture of intracranial arteries.

It can also compress cervical sympathetic plexus, causing Horner syndrome. Horner syndrome is characterized by a classic triad of ipsilateral ptosis, miosis, and anhidrosis.

**Figure 2.4: mediastinal mass***

Large mediastinal mass that can compress superior vena cava are

- Thymoma
- Burkitt’s lymphoma
- Primary lung cancer like small cell carcinoma (most common cause of SVC syndrome)

You cannot distinguish them on chest x-ray. Additional investigations like biopsy are required to confirm the source.
PRELOAD

- Preload is the load on ventricular muscle at the end of diastole. It is determined mainly by the left ventricular end diastolic volume and left ventricular end diastolic pressure, in other words - by venous return.

- The increase in preload will cause an increase in contractility, which subsequently lead to a rise in stroke volume and ejection fraction.

- The increase in pulmonary capillary wedge pressure is evidence of increased preload. In mitral stenosis or mitral valve prolapse, it is not a good index of left ventricular preload because of backward congestion leading to pulmonary edema.

- Chronic increase in preload can lead to dilated cardiomyopathy.

![Figure 3.1: effects on the ventricular preload](image)

STROKE VOLUME

- Stroke volume is the amount of blood that heart pumps out with each beat. It is directly proportional to contractility of the heart and inversely proportional to afterload.

- Stroke volume is calculated as -

\[
SV = EDV \text{ (End Diastolic Volume)} - ESV \text{ (End Systolic Volume)}.
\]
EJECTION FRACTION

- Ejection fraction is the portion of blood that heart pumps out during one contraction, which is usually 60-70% in the healthy normal adult.
- Ejection fraction is calculated as:
  
  **Ejection Fraction** = stroke volume/end diastolic volume

  Now, SV = EDV – ESV, and therefore, EF = EDV – ESV/EDV

- For example; If the SV is 70 ml and EDV is 120 ml in 70kg man. Therefore, ejection fraction is 60% in this individual.

CARDIAC OUTPUT

- Cardiac output is the amount of blood that heart pumps out during 1 minute.
- Cardiac output is calculated as **CO** = heart rate * stroke volume.

  For example; If the heart rate is 72/min, and stroke volume is 70 ml. Therefore cardiac output in 1 minute = 5000ml or 5 L/min.

- According to the Fick’s principle, **CO** = rate of oxygen consumption / arterial oxygen content – venous oxygen content.

AFTERLOAD

- Afterload is the pressure against which heart will work. It is determined by peripheral arterial resistance.
- Chronic increase in afterload (e.g. hypertension, increasing age) will lead to left ventricular hypertrophy. Peripheral resistance is calculated as -

  **Blood flow** = pressure/resistance (Q=P/R), therefore **R** = P/Q

  Resistance is inversely proportional to the 4th power of the radius of the vessel.

  If the resistance will increase, then the blood flow will decrease and the heart will have to do more work to pump out blood against more resistance.

  Chronically it will lead to systolic dysfunction (impaired contractility) and diastolic dysfunction (impaired ventricular relaxation).

- Hypotension occurs when afterload is decreased (e.g. septic shock)
Autoregulation mechanism dominates over extrinsic mechanism (neuronal and hormonal influences). Because the gastrointestinal system does not have dominant autoregulation system, their vessels will constrict under SNS activity, and therefore, blood flow decreases to the gastrointestinal system during exercise.

1) **Coronary circulation**: auto-regulated by endogenous *adenosine and nitric oxide*. When the heart is under stress, more ATP will be used up, and adenosine will form as a byproduct. Adenosine dilates coronary vessels and provides sufficient blood flow to the heart to meet its energy requirements.

2) **Cerebral circulation**: brain maintains its circulation mainly by arterial carbon dioxide level (PaCO$_2$). During exercise, cerebral circulation is unchanged because exercise will increase the level of venous blood carbon dioxide level, which subsequently undergoes pulmonary oxygenation before reaching to the brain.

3) **Skeletal muscle (during exercise only)**: skeletal muscle during exercise regulate its blood flow with the help of myogenic stretch receptors (pressure related) and vasodilator metabolites like lactate. In resting muscle, flow is controlled mainly by the sympathetic nervous system (alpha-1 and beta-2 receptors).

4) **Renal blood flow**: blood flow to the kidney is also commonly considered as autoregulation even though neuronal and hormonal influences partially control it. During hypertension, renal afferents will constrict and maintains its blood flow to the kidney. Chronically, it will lead to hypertensive nephropathy.

5) **Cutaneous blood flow**: heat causes vasodilation and cold temperature causes vasoconstriction. During fever and exercise, there is an increase in heat loss which causes flushing due to vasodilation.

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>CHANGE IN BLOOD FLOW DURING EXERCISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>Increases</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Increases</td>
</tr>
<tr>
<td>Cerebral</td>
<td>No change</td>
</tr>
<tr>
<td>Renal</td>
<td>Decrease</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decrease</td>
</tr>
<tr>
<td>Exercising muscle</td>
<td>Increases</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Increases</td>
</tr>
</tbody>
</table>

*Table 3.1: changes in blood flow to various organ systems during exercise*
HYPERTENSION

High blood pressure is said to be present if it is persistently at or above 140/90 mmHg in adults. The higher number corresponds to systolic pressure while lower numbers correspond to diastolic pressure.

Decisions about aggressiveness of treatment are made according to the classification

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SYSTOLIC (mmHg)</th>
<th>DIASTOLIC (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 120</td>
<td>Less than 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3 (hypertensive crisis)</td>
<td>Higher than 180</td>
<td>Higher than 110</td>
</tr>
</tbody>
</table>

Table 4.1: classification of hypertension

Prehypertension is not considered abnormal, however, advise your patient for lifestyle modifications.

Primary (essential) and secondary hypertension -

- Primary (essential) hypertension is the most common cause of hypertension (95% cases). It is diagnosed when there are no identifiable secondary cause.

- Secondary hypertension is diagnosed when hypertension is due to some underlying secondary cause (5-8% cases).

PATHOGENESIS

1. Systolic Blood Pressure (SBP)

SBP correlates with stroke volume and the compliance of the aorta.

- Stroke volume is directly proportional to contractility of the heart. An increase in the contractility of the heart will cause an increase in cardiac output.
Compliance of vessels decreases with age because of reduced elasticity of the aorta. The decrease in compliance of arteries is the mechanism for systolic hypertension in an individual >60 years of age.

Systolic blood pressure will rise with an increase in preload, contractility, and decrease in compliance of the aorta and vice versa.

2. Diastolic Blood Pressure (DBP)

DBP correlates with the volume of blood in the aorta during diastole. Diastolic blood pressure will rise with an increase in peripheral vascular resistance, blood viscosity, and heart rate.

- DBP increases with vasoconstriction of the arterioles due to the increase in the volume of blood present in the artery during diastole.
- Increase in blood viscosity is seen in polycythemia, leukemia, dehydration while decrease in blood viscosity is seen in anemia, hyper-hydration
- Factors that constrict arteriole smooth muscle cells are α-adrenergic stimuli, catecholamine, angiotensin II, vasopressin, endothelin, and high total body sodium.
- Sodium is one of the main culprits behind hypertension. It causes fluid retention and also damages vascular endothelium producing vasoconstriction due to the release of endogenous amines.

ETIOLOGY

**Primary hypertension:** the most common cause of hypertension is essential hypertension (95% cases of hypertension).

- Environmental or genetic cause.
- Stress: people under stress may overeat or eat a less healthy diet, put off physical activity, drink, smoke or misuse drugs, also leads to the release of stress hormone in circulation.
- High alcohol intake
- Insulin resistance: common in obesity and is a component of ‘metabolic syndrome’.
- Premature baby (low birth weight), maternal smoking and lack of breastfeeding, chewing tobacco, elevated LDL
- Obesity and lack of exercise: excess weight will increase strain on the heart, raises blood cholesterol and triglyceride levels. It will also increase the risk of diabetes. Losing as little as 10 to 20 pounds can help lower your blood pressure and your heart disease risk
- Age: greater than 55 years for men or greater than 65 years for women
THUNDERNOTE: OBSTRUCTIVE SLEEP APNEA

- OSA is the most common type of sleep apnea in elderly and obese population.
- It is characterized by repetitive pauses in breathing during sleep despite the effort to breathe. Sleep apnea is potentially a life-threatening sleep disorder in which tissues in the throat collapses and block the airway. Brain forces the sleep-awake cycle enough to cough or gulp air and open the trachea and this whole cycle starts all over again in the next episode.
- There are pauses in breathing during sleep can contribute to severe fatigue during the day and make it difficult to perform tasks that require alertness. Individuals will have reduction in blood oxygen saturation.
- Hypertension is almost always present in individual with OSA.
- Ask the patient to avoid alcohol and smoking. Advice to lose weight in obese individuals.
- Continuous positive airway pressure is use for moderate to severe apnea or if the above management fails.

Secondary Hypertension: occurs due to pre-existing pathology:

1) Renal disease (3-5% cases)
   - Polycystic kidney disease: multiple cysts in the kidney.
   - **Fibromuscular dysplasia** (most common in younger females): it is a developmental defect of the blood vessel wall that results in an irregular thickening of large and medium-sized arteries and thus causing a stenosis-like condition.
     Renal artery is most commonly affected which will reflexively cause activation of the renin-angiotensinogen system. Bruits can be heard due to renal artery stenosis.
     Doppler ultrasound can be used for diagnosing renal artery stenosis. Most accurate is angiogram. Treatment is renal artery angioplasty and stenting.
   - Chronic kidney disease: glomerulonephritis, diabetic nephropathy.
   - Urinary tract obstruction: kidney stones, Proteus infection (struvite stones), congenital malformations and other conditions that can obstruct the outflow.
   - The renin-producing tumor will lead to high levels of renin.
• **Liddle syndrome (pseudo-hyperaldosteronism):** severe hypertension associated with low plasma renin activity, metabolic alkalosis, hypokalemia and normal to low levels of aldosterone.

Liddle syndrome involves abnormal kidney function, with excess reabsorption of sodium and loss of potassium and hydrogen ions from the renal tubules.

It is treated with a combination of low sodium diet and potassium-sparing diuretic drugs.

2) **Endocrine conditions (1-2% cases)**

• Cushing’s syndrome: high level of mineralocorticoids.

• Hypothyroidism

• Pheochromocytoma: tumor of the adrenal medulla which causes episodic hypertensive crisis.

• Neuroblastoma: high level of catecholamine.

• 11-hydroxylase deficiency: high level of deoxycorticosterone (acts like aldosterone) and sex hormones (hirsutism).

• Acromegaly: increase in growth hormone level in adulthood.

• Conn’s syndrome: primary hyperaldosteronism resulting in hypokalemia.

3) **Vascular conditions**

• Increasing age: systolic hypertension due to decreased elasticity of the aorta in the elderly population.

• Coarctation of aorta: narrowing in the arch of the aorta will cause high blood pressure in upper extremities and low blood pressure in lower extremities. This results in under perfusion of the kidney resulting in an activation of RAS system.

• Vasculitis: inflammation of vessels (increases total peripheral resistance by narrowing vessels)

• Collagen vascular disease: occurs when problems with the immune system affect the collagen. This causes arthritis and inflammation of arteries in the tissues that connect joints and other tissues. It can be seen in ankylosing spondylitis (HLA-B27 serotype), dermatomyositis, rheumatoid arthritis (HLA-DR 3, HLA- DR 4 serotype), SLE, and other immune-mediated diseases.
4) **Epigenetic phenomena**: DNA methylation and histone modification.

- High-salt diet appears to unmask nephron development caused by methylation. Maternal water deprivation and protein restriction during pregnancy increase renin-angiotensin expression in the fetus.
- Mental stress induces a DNA methylation, which enhances autonomic responsiveness. The pattern of serine protease inhibitor gene methylation predicts preeclampsia in pregnant women.

5) **Oral contraceptives**: activates renin-angiotensinogen system because hepatic synthesis of angiotensinogen is induced by the estrogen component of oral contraceptives. The best way to manage this cause of hypertension is to stop oral contraceptives and hypertension goes away in 6 months.

6) **Exogenous steroids**: increases blood pressure by volume expansion.

7) **NSAIDs**: blocks both cyclooxygenase-1 (COX-1) and COX-2 enzymes. COX-2 has a natriuretic effect. The inhibition of COX-2 can inhibit its natriuretic effect. NSAIDs also inhibit the vasodilation effects of prostaglandins at renal afferents and produces vasoconstriction factor (endothelin-1).

8) **Neurogenic causes**: brain tumor, bulbar poliomyelitis, intracranial hypertension

9) **Drugs and toxins**: alcohol, cocaine, cyclosporine, tacrolimus, NSAIDs, erythropoietin, adrenergic medications, decongestants containing ephedrine, herbal remedies containing licorice or ephedrine.

10) **Smoking**: causes vasoconstriction and damages arteries leading to atherosclerosis, thromboangitis obliterans, Raynaud’s phenomenon.

11) **Pregnancy**: gestational hypertension (new onset hypertension that develops after 20th week of pregnancy), pre-eclampsia (hypertension + proteinuria) or eclampsia (hypertension + seizures)
CLINICAL PRESENTATION

Hypertension is usually an asymptomatic condition.

- **Headache**: The best evidence indicates that high blood pressure does not cause headaches except perhaps in the case of hypertensive crisis (blood pressure > 180/110 mmHg).
  
  According to one study, people with high blood pressure seem to have significantly fewer headaches than the general population. The higher is the pulse pressure, the stiffer is the blood vessels. In the stiffer blood vessel, there is less chance of nerve endings working properly. If the nerve endings aren't functioning correctly, there is less chance that person might feel pain.

  In other words, headache is not a reliable symptom of hypertension. Other findings that might be present in chronic hypertension are:

  - Fatigue, confusion and vision problems
  - Chest pain and difficulty breathing
  - Blood in the urine
  - Pounding in your chest, neck, or ears
  - Symptomatic nosebleeds (nose picking is most common cause of nosebleeds)

A variety of symptoms may be indirectly related to hypertension but are not always caused by it, such as:

- Blood spots in the eyes or subconjunctival hemorrhage, facial flushing and dizziness

COMPLICATION

- **Left ventricular hypertrophy** (most common overall complication)
- **Acute myocardial infarction** (most common cause of death)
- **Atherosclerosis**
- **Intracerebral hematoma** (due to rupture of Charcot-Bouchard aneurysms)
- **Subarachnoid hemorrhage** (due to rupture of a berry aneurysm)
- **Lacunar infarcts** (small infarcts due to hyaline arteriolosclerosis). Common location of lacunar infarcts includes basal ganglia, pons, internal capsule, thalamus and cerebral white matter.
- Benign nephrosclerosis (atrophy of tubules and sclerosis of glomeruli occurs due to hyaline arteriolosclerosis)
- Malignant hypertension (rapid increase in blood pressure accompanied by renal failure and cerebral edema)
- Hypertensive retinopathy (arteriovenous nicking, hemorrhage of retinal vessels, retinal infarction, papilledema)

**MANAGEMENT**

- Lifestyle modification is always the first step in the management of hypertension. It is usually recommended for 3-5 months for mild hypertension. Start medical therapy if not controlled.
- The goal of hypertension control in diabetic hypertensive or patient under the age of 60 is 140/90 mmHg. The goal of hypertension in age greater than 60 is 150/90 mmHg.
- The goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality, with the focus on controlling the systolic blood pressure. Most patients will achieve diastolic pressure control when the systolic blood pressure control is achieved.
- Exogenous salt intake should be limited to approximately 5 to 6 g per day.
Body-mass index (BMI) should be reduced to 25 kg/m² and waist circumferences should be reduced to less than 102 cm in men and less than 88 cm in women. Decreasing the BMI is most effective way of lifestyle modification and management of hypertension.

The patient is advised to do regular aerobic exercises and follow relaxation techniques like yoga.

Ambulatory blood pressure monitoring should be incorporated.

Diuretics like thiazides are the first line of drug for management of hypertension with some exceptions:
- Diabetics: ACE inhibitors are the first line of drug
- Benign prostatic hyperplasia: alpha-blockers
- Migraine headache: beta blockers, calcium channel blockers
- Pregnancy: labetalol, methyldopa, hydralazine (for acute reduction)

For a patient whose blood pressure is more than 20 mmHg above the systolic pressure goal or more than 10 mm Hg above the diastolic pressure goal, initiation of therapy using 2 agents, one of which usually will be a thiazide diuretic, should be considered.

If the 2 drugs combination fails to control blood pressure, add a 3rd drug. Suspect secondary hypertension if 2 or 3 drugs fail to control primary hypertension.

Effective combination therapies include thiazide diuretics with ACE inhibitors or ARBs (angiotensin receptor blocker) or calcium blockers. calcium-channel antagonists with ARBs or ACE inhibitors. The point here is, do not combine ACE inhibitors with ARBs because of the risks of hyperkalemia, low blood pressure, and kidney failure.

Although additional data is needed, renal denervation is a promising therapy in the treatment of resistant hypertension.
CHAPTER 5 – VENOUS PATHOLOGY

VENOUS SYSTEM OF LEG

Greater and lesser saphenous veins (superficial veins) joins with a femoral vein (deep vein) at the saphenofemoral junction that forms an external iliac vein.

The external iliac vein will drain into a common iliac vein and then to inferior vena cava. Generally, the blood flows from superficial veins to deep vein.

As deep veins have higher pressure than superficial, valves present in veins prevent reversal of blood flow.

**Figure 5.1:** anatomy of venous system of legs

VARICOSE VEINS

PATHOGENESIS

- The vein is dilated and tortuous (twisted) due to valve incompetence that results in reversal of blood flow from the deep veins to the superficial vein.
- It can also occur due to any obstruction in a venous system such as deep venous thrombosis. Reversal of flow will generate high pressure backward resulting in dilation of the veins.

RISK FACTORS

- Female gender
- Family history
- Multiple pregnancies
- Jobs with prolonged standing
- Obesity
- Elderly population
LOCATION

- Most common site is a superficial saphenous vein. However, it can be present in any venous system.

**Figure 5.2:** large visible varicose vein. **Figure 5.3:** tortuous (twisted) vein

CLINICAL PRESENTATION

- Skin thickening (lipodermatosclerosis)
- Large visible tortuous vein that can be visible just underneath the skin
- Ulceration
- Ache, heavy legs and ankle swelling (often worse at night and after exercise)
- Telangiectasia

COMPLICATION

Most varicose veins are benign, but severe varicosities can lead to major complications due to the poor circulation through the affected limb.

- Inability to walk
- Stasis dermatitis and venous ulcers especially near the ankle
- Severe bleeding from minor trauma
- Superficial thrombophlebitis (more serious problem if extended into deep veins)
- Acute fat necrosis

INVESTIGATION

- Confirm by duplex ultrasound, venography
MANAGEMENT

Compression hosiery is not the best but **is the best initial management**. It can help temporarily by keeping the veins empty. It includes support stocking, Ace bandages, or Unna boot. Varicose veins are treated with interventional therapy such as:

- Endothermic ablation and endovenous laser treatment of greater saphenous vein.
- If endothermal ablation is unsuitable, offer ultrasound guided foam sclerotherapy (medicine is injected, which makes varicose vein shrink).
- If foam sclerotherapy is unsuitable, offer surgery: **ligation and stripping** (removal of the vein is not a major problem because superficial vein drains only about 10% of the blood from the legs). Consider treating incompetent varicose tributaries at the same time.

**THUNDERNOTE: PORTAL HYPERTENSION**

- Portal hypertension is a high pressure in the hepatic portal venous system.

**Cause**

- Pre-hepatic (portal vein thrombosis, congenital atresia)
- Intra-hepatic (liver cirrhosis, fibrosis)
- Post-hepatic (due to cardiac problems like right heart failure, constrictive pericarditis)

**Clinical Presentation**

- Ascites
- Anorexia, fatigue, nausea, vomiting
- Hepatic encephalopathy
- Splenomegaly
- Gastric varicosities (dilated sub mucosal veins in stomach) and esophageal varicosities (dilated submucosal veins in lower 1/3rd esophagus). Both have high tendency to bleed, diagnosis by endoscopy.
- Anorectal varicosities (not to be confused with hemorrhoids which are due to prolapse in venous plexus of rectum) and caput medusa (which is present at the level of umbilicus)
EVALUATION OF CHEST PAIN

Any elderly patient who presents with anginal chest pain (dull, squeezing substernal chest pain) must be evaluated for acute coronary syndrome.

If the patient is hemodynamically stable, obtain focused history, assess vital signs and perform chest x-ray and ECG. Administer aspirin if the risk of aortic dissection is low.

- If ECG is consistent with ST-elevated myocardial infarction, best initial step in management is emergency thrombolysis or PCI unless contraindicated.
- If ECG is consistent with non-ST-elevated myocardial infarction, best initial step in management is low molecular weight heparin.

If the ECG findings are inconsistent with acute coronary syndrome, check chest x-ray, cardiac markers and risk stratify for acute coronary syndrome. Assess for pulmonary embolism, pericarditis, aortic dissection and treat appropriately. Details are discussed in subsequent chapters.

The most common cause of chest pain in elderly population is gastroesophageal reflux disease. If the cardiac markers are normal and risk for acute coronary syndrome is low, suspect gastroesophageal reflux disease.

ISCHEMIC HEART DISEASE

- Ischemic heart disease is due to an imbalance between myocardial oxygen demand and supply from the coronary arteries.
- Coronary artery disease is the number one cause of death in the United States. Ischemia occurs secondary to the coronary artery disease.
- Atherosclerosis is the number one cause of coronary artery disease.
- Hypertension is the number one cause for atherosclerosis while diabetes and smoking are the most dangerous causes for coronary artery disease.

STABLE ANGINA

- Main cause: atherosclerotic occlusion of the coronary arteries (>70%).
- The appearance of anginal chest pain occurs during exertions like exercise, climbing staircase or emotional stress.
- Patient often complains of sub-sternal chest tightness-heaviness and dull-sore-squeezing sub-sternal pain that may radiates to the neck or left arm (because the sympathetic fibers from T1-T2 will supply both the heart and left arm, jaw).
- Pain disappears by rest or sublingual nitroglycerine.
UNSTABLE ANGINA

- Unstable angina is also called as acute coronary syndrome. It will have all symptoms of anginal chest pain at rest.
- Chest discomfort does not improve with nitroglycerine or recurs soon after nitroglycerine.
- The lumen of the coronary artery is not completely occluded by the thrombus. It has a high risk for myocardial infarction. Irreversible changes in cardiac myocytes begins after 20-25 minutes of ischemia.

PRINZMETAL ANGINA

- Chest pain occurs due to the episodes of coronary artery vasospasm. Atherosclerotic narrowing of lumen is not present.
- A possible mechanism behind this is an increase in platelet thromboxane A2 and endothelin (a potent vasoconstrictor).
- Prinzmetal angina produces chest pain at rest; more commonly in the morning on waking up.
- Unlike unstable angina, Prinzmetal angina will be relieved by nitroglycerine.
- Calcium channel blockers are preferred over the beta-blockers in the management.
- During the episodes, transmural ischemia will occur that will cause ST-segment elevation on ECG.

MYOCARDIAL INFARCTION

- Myocardial infarction will present similarly to unstable angina. It is not possible to distinguish between them solely base on clinical presentation. Positive cardiac enzyme test is indicative of MI.
- Lumen of the coronary artery is completely occluded due atherosclerotic plaque rupture and superimposed thrombus formation or coronary artery spasm.
- Serum cardiac markers will be released into the blood due to cell lysis/death. Cardiac markers will not be present in blood if cardiac myocyte is not dead.
RISK FACTOR

- Age (male > 55 years, female > 65 years) is the most important risk factor. There is less than 2% chance of having MI in a young woman at age 25 compared to 65-year-old female.
- Family history: multiple gene inheritances.
- Lipid abnormalities: leads to atherosclerosis; LDL > 160 mg/dl, HDL < 40 mg/dl.
- Environmental: smoking, lifestyle, drugs (cocaine); hypertension and diabetes.
- Previous myocardial infarction
- Congestive heart failure, mitral valve dysfunction, aortic dissection, aortic aneurysm
- Atrial or ventricular arrhythmia
- Hypercoagulable states (polycythemia, antithrombin III deficiency)
- Vasculitis (polyarteritis nodosa, Kawasaki disease)

DIFFERENTIAL DIAGNOSIS

- Gastroesophageal reflux disease and peptic ulcer disease is the most common cause of epigastric pain. Pain is related to certain food, and relieved by antacids.
- Stable angina (pain on exertion, ST segment depression)
- Unstable angina (pain at rest, ST segment depression)
- Diffuse esophageal spasms (normal ECG, abnormal gastrointestinal series)
- Pericarditis (diffuse ST-segment elevation, PR depression, pain relieved on leaning forward)
- Pulmonary embolism (pleuritic chest pain, prolonged immobilization)
- Costochondritis (tenderness on palpation)
- Aortic dissection (pain radiating to the back, widened mediastinum)
- Tension pneumothorax (absent breath sound on affected side, often post-trauma)
- Prinzmetal angina (pain at rest, ST elevation during episodes)
POST MI COMPLICATIONS

- Cardiac arrest: most commonly occurs due to the ventricular fibrillation and is the most common cause of death following an MI.

- Bradyarrhythmia: atrioventricular block is more common following inferior wall MI.

- Pericarditis: acute pericarditis in the first 48 hours following a transmural MI is common (10% cases).

- Left ventricular free wall rupture: this is seen in around 3% cases of MI and occurs after 5-7 days. The patient will present with acute heart failure secondary to cardiac tamponade (raised JVP, pulsus paradoxus, diminished heart sounds). Urgent pericardiocentesis and thoracotomy are required.

- Ventricular septal defect: rupture of the interventricular septum usually occurs in the first week and is seen in around 1-2% of patients. An echocardiogram is diagnostic and will exclude acute mitral regurgitation, which presents in a similar fashion. Urgent surgical correction is needed.

- Acute mitral regurgitation: more common with posterior wall infarction and occurs due to the rupture of the papillary muscle. An early-to-mid systolic murmur is typically heard. Emergency surgical repair is required. Anything that has an acute presentation in the heart carries bad prognosis and must be treated emergently.

- Cardiogenic shock: if a large part of the ventricular myocardium is damaged in the infarction, ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock. Other causes of cardiogenic shock include 'mechanical' complications such as left ventricular free wall rupture.

- Congestive heart failure: If the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure.

- Left ventricular aneurysm: the ischemic damage sustained may weaken the myocardium resulting in aneurysm formation. This is typically associated with persistent ST elevation and left ventricular failure. The thrombus may form within an aneurysm increasing the risk of stroke.

- DRESSLER SYNDROME: It is an immune-mediated pericarditis that can occur several weeks after an MI.

  **Pathogenesis:** the underlying pathophysiology is thought to be an autoimmune reaction against the antigenic proteins on the myocardium.

  **Clinical presentation:** the patient often describes the pain that is worse with deep inspiration and improves on leaning forward.
**Diagnosis:** clinical presentation and ECG findings of normal QRS complex, ST-segment elevation and PR-depression in all leads (reciprocal in lead V1).

**Management:** the best initial management of Dressler’s syndrome is NSAIDs.

<table>
<thead>
<tr>
<th>Time</th>
<th>Microscopic Change</th>
<th>Gross Change</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 hours</td>
<td>No change</td>
<td>No change</td>
<td>Cardiogenic shock, congestive heart failure, arrhythmia</td>
</tr>
<tr>
<td>24-hours</td>
<td>Coagulative necrosis (removal of nucleus; pyknosis, karyorrhexis, karyolysis)</td>
<td>Dark discoloration</td>
<td>Arrhythmia (due to damage in conductive pathway), If no arrhythmia within 24 hours of MI, 90% less probability of having one later.</td>
</tr>
<tr>
<td>1-3 days</td>
<td>Numerous neutrophils (due to acute inflammation following necrosis)</td>
<td>Yellow discoloration</td>
<td>Fibrinous pericarditis (transmural infarctions)</td>
</tr>
<tr>
<td>3-7 days</td>
<td>Numerous macrophages (will clean up the necrotic debris). The infarcted wall is weakest around this time.</td>
<td>Yellow pallor</td>
<td>Ventricular free wall rupture (leads to cardiac tamponade), interventricular septum rupture (left to right shunt), Papillary muscles rupture (mitral insufficiency)</td>
</tr>
<tr>
<td>2 weeks</td>
<td>Granulation tissue with fibroblast, collagen and blood vessels (reconstruction of infarcted wall)</td>
<td>Central pallor with red border</td>
<td>-</td>
</tr>
<tr>
<td>1 Month</td>
<td>Fibrosis (scar formation)</td>
<td>White discoloration</td>
<td>Aneurysm, Dressler syndrome</td>
</tr>
</tbody>
</table>

Table 6.1: Post-MI changes
**Figure 6.1**: wavy fibers (1-4 hours) *

**Figure 6.2**: papillary muscle rupture (1-week) *

**Figure 6.3**: left ventricular aneurysm (1-month) *

**Figure 6.4**: scar tissue (1-month) *
Post-MI ECG Changes in STEMI

- Unstable angina (before the actual MI): T wave inversion
- **Within hours after MI: marked ST-segment elevation + upright T wave**
  - After 24 hours: Significant Q wave + ST-segment elevation + upright T wave
  - After 48 hours: Significant Q wave + less ST-segment elevation + inverted T wave
  - After 1-2 weeks: Significant Q wave + No ST-segment elevation + inverted T wave
  - After 1-2 months: Significant Q wave only

**ST-SEGMENT ELEVATION**

ST elevation >1mm in the limb leads and >2mm in the chest lead indicates an evolving acute MI until there is proof to the contrary. ST-segment elevation can also be present in:

- Early ventricular repolarization (normal variant in young adults)
- Pericarditis
- Ventricular aneurysm
- Pulmonary embolism
- Intracranial hemorrhage

**ST-SEGMENT DEPRESSION**

Non-ST-segment elevated MI (NSTEMI) are difficult to distinguish from unstable angina on ECG. Cardiac markers are elevated in NSTEMI while cardiac markers are normal in unstable angina. ST-segment depression can be present in:

- Myocardial ischemia
- Unstable angina
- Left ventricular hypertrophy
- Intraventricular conduction defects
- Medications (digitalis)
- Reciprocal changes in leads opposite to the area of acute injury (lead V1)
12-LEAD ECG INTERPRETATIONS

Figure 6.5: coronary arteries and 12-leads*

- **Left circumflex artery** supply blood to lateral wall of left ventricle, left atrium and left posterior fasciculus of left bundle branch. Occlusion will cause lateral wall MI. Reciprocal ST depression in inferior leads (III and vVF).

- **Left anterior descending** artery supply blood to anterior wall of left ventricle, anterior 2/3 rd interventricular septum, bundle of his, right bundle branch and left anterior fasciculus of left bundle branch. Occlusion will cause septal MI.

- **Right coronary artery** supply blood to right atrium, right ventricles, posterior and inferior wall of left ventricle. Occlusion will cause inferior wall MI (commonly seen together with posterior wall MI)
Figure 6.6: inferior wall MI*

Figure 6.7: anterior wall MI*

Figure 6.8: lateral wall MI*
PHYSICAL EXAMINATION

- Normal in the absence of an anginal attack.
- MI is diagnosed if the anginal attacks occur more than 20 minutes.
- Look for heart failure signs (shortness of breath, increased JVP, bibasilar crackles, edema in legs) from prior MI.
- Rule out other possible causes of chest pain such as costochondritis, pericarditis.

PRETEST PROBABILITY OF CORONARY ARTERY DISEASE

- <10% probability in asymptomatic patient and woman less than 50 years with atypical angina: **do nothing.**
- 10-90% probability in men with atypical chest pain and age more than 50 years: **do stress test if ECG is normal.**
- >90% probability in woman greater than 60 years with typical chest pain (angina-like) or a man older than 40 years with typical angina: **If ECG is normal, go directly to angiography.**

DIAGNOSIS

- Best first step in patient’s with moderate to severe probability of having acute coronary syndrome is always an ECG.
- If ECG is inconclusive (NSTEMI can have ST depression or normal), go for a exercise stress test or thallium echo (don’t give dipyridamole in patients with reactive lung disease and it is generally not preferred when exercise stress test is a possible alternative). Both tests are equivalent.
- If ECG test shows STEMI or for individuals with high probability, a coronary angiogram can be used to definitively diagnose or rule out coronary artery disease.
- Coronary angiography should be performed **after stabilizing a patient** with medical therapy, but emergency angiography may be undertaken in unstable patients.
- In patients with unstable angina/NSTEMI, the TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision-making.
- For prinzmetal angina, ST elevation on ECG is not specific. Angiography is done to exclude possible acute coronary syndrome. Prinzmetal angina can be suspected when angiogram is normal.
Figure 6.9: Coronary angiogram showing a total occlusion of left anterior descending artery and a normal left circumflex coronary artery (LCX). Angioplasty restored flow with distal filling defects due to a residual thrombus.

Cardiac Markers:

- Myoglobin: it is detected from 1 to 5 hour of chest pain.
  
  Normal myoglobin means no MI, however if myoglobin is elevated, it is non-specific; It can be MI or something else. No Troponins or CK-MB will be detected until 4-7 hours of an onset of acute MI.

- Troponin I will start rising by 4th hour, peaks at 16 hours and remain elevated for 7-10 days (usually drawn every 8 hours three times till MI is ruled out)

- Creatinine Kinase-MB will start rising by 4th hour, peaks at 20 hours and disappears on the 3rd day of an acute MI. It is used to detect re-infarction because troponin level will be high for 10 days.

- CK-MB have sensitivity and specificity of 95%. Troponin I is more specific than CK-MB because CK-MB can also be elevated in rhabdomyolysis, myocarditis or other conditions (differentiated based on clinical presentation).

  Troponin I along with CK-MB improves overall sensitivity and specificity for MI.
MANAGEMENT

- Any patient with moderate-severe probability of acute coronary syndrome, who complains about pain typical for angina, give aspirin and nitroglycerine (given sublingually or by spray) as soon as possible even before performing an ECG or placing IV access line.

ACUTE MANAGEMENT FOR STEMI

- The decision must be made quickly as to whether the patient should be treated with thrombolysis or with primary percutaneous coronary intervention (PCI).

  PCI is superior to thrombolytic (mortality benefits, less chance of developing post-MI complications, fewer complications like hemorrhage).

- In the absence of contraindications, give thrombolytic (tissue plasminogen activator) within 12 hours of anginal attack. Ideally, thrombolytic medications should be given within first 30 minutes of patient's arrival at the hospital. After thrombolytic therapy, patient must be transferred for angiography.

- If pain persists after initial thrombolytic therapy, schedule the patient for PCI.

- GP IIb/IIIa inhibitors such as abciximab or eptifibatide or tirofiban is added to aspirin after PCI to prevent a clot.

- Placement of stents coated with sirolimus/paclitaxel decreases the risk of restenosis (by 90%) as compared to bare metal stents (75-80%). Clopidogrel is given for 1-year in patients with stents coated with sirolimus/paclitaxel and for 1-month for bare metal stents.

ACUTE MANAGEMENT FOR NSTEMI

- NSTEMI patients are not a candidate for immediate thrombolytic. Thrombolytics such as streptokinase, and tissue plasminogen activator are not helpful in NSTEMI and is not preferred.

- They should receive anti-ischemic therapy; low molecular weight heparin and if pain persists then may be candidates for PCI urgently or during admission.
THUNDERNOTE: CONTRAINDICATIONS FOR THROMBOLYTICS

Absolute contraindication

- History of intracranial hemorrhage
- Ischemic stroke within 3 months
- Cerebral structural lesions
- Malignant intracranial neoplasm
- Intracranial surgery within 2 months
- Active bleeding or bleeding diathesis (except menses)
- Uncontrolled hypertensive emergency

Relative contraindications (give thrombolytic if benefits outweigh the risk and PCI is not available):

- Hypertensive crisis
- Major surgery less than 3 weeks previously
- History of Ischemic stroke before 3 months
- Recent internal bleeding within 4 weeks
- Pregnancy
- Current warfarin use

INDICATIONS FOR PCI and CABG

- PCI like angioplasty is indicated if 1 coronary vessel is occluded other than the main left coronary artery.

- CABG is more effective when 2 vessels with serious risk factors such as diabetes, 3 vessels or left main coronary artery are occluded (saphenous vein, Internal thoracic artery are frequently used).

- In 2 or 3 vessel disease, if right coronary artery (inferior wall MI) is involved, we first do stenting emergently in right coronary artery and then schedule the patient for CABG. CABG is rarely done in an emergency. When harvesting is done, the patient is given heparin to prevent the blood from clotting.
LONG TERM MANAGEMENT

- All patients with acute MI should receive aspirin and prasugrel (better choice than clopidogrel) in the absence of any contraindication.

  In patients with aspirin allergy: use clopidogrel

  If both aspirin and clopidogrel fails: use ticlopidine.

- High-intensity statin therapy is given to everybody. The goal is to maintain LDL level less than 100mg/dL.

- Sublingual nitroglycerin to is given to abort angina attacks. Advise the patient; when and how to take it.

- Beta-blockers are generally used as a first-line rhythm control drug for chronic management.

- Calcium channel blocker like verapamil is used when beta blockers are contraindicated (asthma with wheezing and 2nd degree AV block). Selective beta-blockers like metoprolol are not contraindicated for a patient with the previous history of COPD with no wheezing or difficulty in breathing at the time of presentation. Increase the dose in case of poor drug response [do not stop the drug abruptly because beta-adrenergic receptors are super-sensitized with long term beta blocker therapy].

- If a calcium channel blocker is used as monotherapy, verapamil or diltiazem should be used. If used in combination with a beta-blocker, then use a long-acting dihydropyridine calcium-channel blocker such as nifedipine. Remember that beta-blockers should not be prescribed concurrently with verapamil.

- If a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: a long-acting nitrate, ivabradine, nicorandil, or ranolazine.

- If a patient is taking both a beta-blocker and a calcium channel blocker (dihydropyridine group) then add third drug only when a patient is awaiting assessment for PCI or CABG.

- ACE inhibitors are indicated for all acute MI. They are most effective when ejection fraction is less than 40%. If the patient develops chronic cough on ACE inhibitor, switch it to angiotensin receptor blocker (ARBs).

- Furosemide work favorably and do not interfere with the effects of ACE inhibitors. It is indicated for all patient with high blood pressure and volume overload in failing heart.
POST MI PRECAUTIONS

- Do stress test after 5 days or prior to discharging patient. If the test is positive: recommend not to involve in any sexual activity for 2-6 weeks. Male on the bottom and female on the top is better position in heart failure patients. If the test is negative: he can have sex whenever he wants.

- Do not give nitrates with sildenafil due to the risk of severe hypotension.

- Both beta-blockers and anxiety can cause sexual dysfunction post-MI. Reassure the patient and help him to cope with anxiety.

- Lifestyle change such as weight loss, smoking cessation, low salt diet, aerobic exercise, and healthy diet is recommended.

THUNDERNOTE: INDICATIONS FOR STATIN

Four statin benefit groups which demonstrated a maximum reduction in outcomes associated with atherosclerotic cardiovascular disease (ASCVD) are:

1) Individuals with clinical ASCVD (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, stroke or peripheral arterial disease presumed to be of atherosclerotic origin)

2) Individuals with LDL cholesterol ≥190 mg/dl.

3) Individuals 40-75 years of age with diabetes and LDL cholesterol 100-189 mg/dl without clinical ASCVD.

4) Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl and have an estimated 10-year ASCVD risk of 7.5% or higher (Age >75 without any other risk factors, alone have 10-year ASCVD risk >7.5%)

In selected individuals who does not fall in above 4 categories, whether to initiate statin therapy or not is still unclear. Additional risk factors must be considered.

Recommendations for High-intensity statin therapy:

- All patients with age less than 75 years and have MI, stable/unstable angina, stroke, transient ischemic attack, peripheral arterial disease
- All patients with diabetics with 10-year ASCVD risk >7.5%
- LDL >190mg/dL at any time
**Recommendations for Moderate intensity statin therapy:**

- All patients with **age more than 75 years** and have acute coronary syndrome, MI, stable/unstable angina, stroke, transient ischemic attack, peripheral arterial disease
- Diabetics with 10-year ASCVD risk <7.5%
- Estimated 10-year risk of ASCVD in non-diabetics >7.5%

High-intensity statin therapy is defined as a daily dose that lowers LDL-C by ≥50% and moderate-intensity statin therapy lowers LDL-C by 30%.

Lifestyle modification (healthy diet, regular exercise, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction***.

- High-intensity statins dose: Rosuvastatin 20-40mg daily, Atorvastatin 40-80mg daily
- Moderate-intensity statins dose: Atorvastatin 10-20mg daily, Rosuvastatin 5-10mg daily, Simvastatin 20-40mg daily, Pravastatin 40-80mg daily, Lovastatin 40mg daily.

[** Dosages are not tested on USMLE but it is important to remember indications for high-intensity and low-intensity statin therapy for Step 3]

**REPERFUSION INJURY**

- Reperfusion injury is the tissue damage that occurs when the blood supply returns to the tissue after a period of ischemia or lack of oxygen. It can be observed after thrombolysis for acute-MI, PCI, and CABG.

- The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function.

- Reperfusion injury can cause myocardial stunning, microvascular dysfunction (vasoconstriction; no-reflow after reperfusion therapy) and even death. Histological section will show myofibril thinning and wavy pattern.

- Although, inotropic stimulation is not an ideal strategy to counter reperfusion injury, it is effective and not associated with worsening of injury. Transient inotropic support is routinely used for a stunned re-perfused myocardium in variety of settings, however, there is no definitive therapy.
CLASS I: SODIUM CHANNEL BLOCKERS

Class IA antiarrhythmic

Drugs: Quinidine, Procainamide hydrochloride

- **Mechanism**: act on open or activated state Na+ channel of myocardium.

- Quinidine also blocks muscarinic and alpha receptors, so typical side effect caused by them is called as cinchonism (constipation/diarrhea, tinnitus, ocular dysfunction, CNS excitation, hypotension). It is never the first line drug for any arrhythmia but every medical exam loves to test on it.

- Procainamide: Less muscarinic block compared to quinidine, no alpha block. But, it acts like hapten, and adverse effect include drug-induced lupus in certain group of people who are slow acetylators, hematotoxicity, torsades rhythm. It is used in Wolf-Parkinson-White syndrome and acute ventricular arrhythmias.

- **Effect on ECG**: wide QRS complex and QT interval. No effect on SA/AV node.

Class IB antiarrhythmic

Drugs: Lidocaine hydrochloride

- **Mechanism**: blocks inactivated Na+ channel of myocardium, works best in hypoxic tissues

- **Effect on ECG**: decrease in QT interval, tachycardia, no effect on SA/AV node.

- **Use**: in acute ventricular arrhythmia, digoxin toxicity.

Class IC antiarrhythmic

Drugs: Flecainide, Propafenone

- **Mechanism**: blocks fast sodium channel, especially of His-Purkinje tissue.

- Highly pro-arrhythmogenic. Last choice drugs when all other option fails. Flecainide in combination with procainamide is used in Wolf-Parkinson-White syndrome.

- **Effect on ECG**: prolongs QRS, heart rate is variable.
CLASS II: BETA BLOCKERS

Drugs: metoprolol, acebutolol, propranolol, atenolol, esmolol and others.

- **Mechanism**: blocks beta-adrenergic receptors. They decrease SA and AV nodal activity, and increases diuresis.

- **Effect on ECG**: a small increase in PR interval and decrease in heart rate.

- **Use**: post-MI, angina (except Prinzmetal angina), hypertension, supraventricular tachycardia, thyrotoxicosis, migraine prophylaxis, anxiety.

*Propranolol* is generally used for extra-cardiac manifestations such as thyrotoxicosis, and migraine prophylaxis.

*Esmolol* is the beta-blocker of choice in emergency setting. It is not used for long-term management. Esmolol is used in acute supraventricular tachycardia, and hypertensive emergency.

*Carvedilol* is a direct beta1 and alpha 1 blocker. It will have dual function of vasodilation along with decreases in heart rate.

- **Adverse effect**: bronchospasm, cold peripheries due to vasoconstriction (beta-2 block), fatigue, and hyperglycemia and sleep problems.

  B-blocker overdose will not lead to complete heart block but calcium channel blocker overdose can cause complete heart block.

- **Contraindication**: uncontrolled heart failure, severe asthma (mild asthma is not an absolute contraindication), sick sinus syndrome.

- Concurrent verapamil use may precipitate severe bradycardia and use of beta-blockers with verapamil is discouraged.

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THUNDERNOTE

Theophylline

An end-line anti-asthmatic drug, which will cause bronchodilation by inhibiting phosphodiesterase and increasing cAMP level.

It will block the action of adenosine and higher dose of adenosine is required for adenosine testing in supraventricular tachycardia.

- B-Blockers can be used for theophylline-induced tachyarrhythmia.
- Barbiturates & Benzodiazepines can be used for theophylline-induced seizures.
CLASS III: POTASSIUM CHANNEL BLOCKERS

Drugs: amiodarone, sotalol, dofetilide

- Amiodarone: half-life is more than 80 days. Amiodarone has high tissue binding capacity and cytochrome P450 inhibitor. It increases concentration of digoxin and impairs the metabolism of warfarin, tending to potentiate its anticoagulant effect. It interferes with depolarization (class I antiarrhythmic), has beta blockade effect (class II antiarrhythmic), prolongs repolarization (class III antiarrhythmic), and has calcium channel blockade effect (class IV antiarrhythmic). It is the most effective antiarrhythmic for atrial fibrillation with structural heart disease, and symptomatic ventricular arrhythmias.

Adverse effect: blue pigmentation of the skin, pulmonary fibrosis, corneal deposits, hepatotoxic, thyroid dysfunction, thrombophlebitis, peripheral neuropathy, prolongs QT interval (torsades).

- Sotalol: potassium channel and beta-blocker. Thus, sotalol decreases heart rate and decreases AV conduction also. The most salient feature of sotalol is its short half-life and acts quickly in life-threatening ventricular arrhythmias.

CLASS IV: CALCIUM CHANNEL BLOCKERS

Drugs: verapamil, diltiazem (not used in hypertension management)

- Mechanism: blocks cardiac calcium channel in SA and AV node and decreases its electrical conductivity.

- Adverse effect: heart failure, constipation, hypotension, bradycardia

- Use: SVTs (supraventricular tachycardia), angina (other than prinzmetal angina)

Beta blockers, verapamil and digoxin have additive AV nodal block effect. Combination of digoxin with beta-blockers is appropriate for low ejection fraction due to supraventricular arrhythmias or compensated heart failure, however combination of all 3 drugs is rarely indicated as there is high risk of AV nodal blockage.

Drugs: nifedipine, amlodipine

- Mechanism: blocks calcium channels in vasculature and act as a vasodilator. They will cause reflex tachycardia and can worsen angina due to increase in functionality of heart. Beta blockers are used to block this effect if necessary.

- Use: hypertension, prinzmetal angina and Reynauds phenomenon.

- Adverse effect: flushing, headache, ankle swelling, gingival hyperplasia [phenytoin and cyclosporine also increases risk of gingival hyperplasia in predisposed patients].
OTHER DRUGS

Adenosine

- **Mechanism**: decreases SA and AV nodal activity by decreasing cAMP (hyperpolarize the cell by potassium efflux). Duration of action is 10 seconds only.
- **Use**: It is used for both diagnosis and management of supraventricular tachycardia that do not improve with vagal maneuvers.
- **Drug interaction**: effects of adenosine is enhanced by dipyridamole, dopamine, and carbamazepine requiring lower dose of adenosine. Its effect is competitively blocked by theophylline and caffeine required higher dose of adenosine.
- **Adverse effect**: chest pain, bronchospasm, can enhance conduction down accessory pathways resulting in increased ventricular rate. Asthma, long QT syndrome, and 2nd or 3rd degree heart blocks are absolute contraindications.

Magnesium sulphate

- **Mechanism**: magnesium sulphate decrease the rate of SA node impulse generation, and prolongs the conduction time. It also stabilizes the excitatory membrane and blocks peripheral neuro-muscular transmission.
- **Use**: The first line drug for torsades-de-pointes (stabilizes the membrane), seizures in pregnancy.
- **Adverse effect**: respiratory depression, hypotension, reduced reflexes, hypothermia and pulmonary edema.

Digoxin

- **Mechanism**: digoxin is a cardiac glycoside that increases intracellular calcium by inhibiting cardiac Na-K+ ATPase. Digoxin will increase contractile force of the heart and block AV node by indirectly increasing vagal activity (by inhibiting neuronal Na-K+ ATPase).
- **Use**: congestive heart failure (for low ejection fraction), supraventricular tachycardia (except Wolf Parkinson White syndrome).
- **Monitor potassium level when the patient is on digoxin (digoxin causes hyperkalemia.)**
- **Adverse effect**: hyperkalemia, lethargy, nausea, vomiting, anorexia, confusion, visual disturbances, AV block when taken with beta-blockers or calcium channel blockers.
Drug interaction:

- Factors that increases toxicity of digoxin are **hypokalemia**, increasing age, renal failure, myocardial ischemia, hypomagnesemia, hypercalcemia, hypernatremia, hypoalbuminemia, hypothyroidism.
- Drugs such as amiodarone, quinidine, verapamil, diltiazem, spironolactone compete for secretion in distal convoluted tubule.
- Management of adverse effect: digibind (Fab antibodies toward digoxin) and supportive **electrolyte** therapy.

Atropine

- **Mechanism**: atropine is a competitive antagonist at muscarinic acetylcholine receptor. It dilates the pupils, increases heart rate and reduces secretions such as lacrimation and salivation.
- **Use**: sinus bradycardia, asystole or pulseless electrical activity, organophosphate poisoning.
- **Adverse effect**: tachyarrhythmia, precipitates narrow-angle glaucoma, dry mouth.
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