

Clinical pharmacology

Beta blockers

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Locations of Beta-adrenergic receptors

Receptors

Location

Beta 1

Heart , kidney , brain

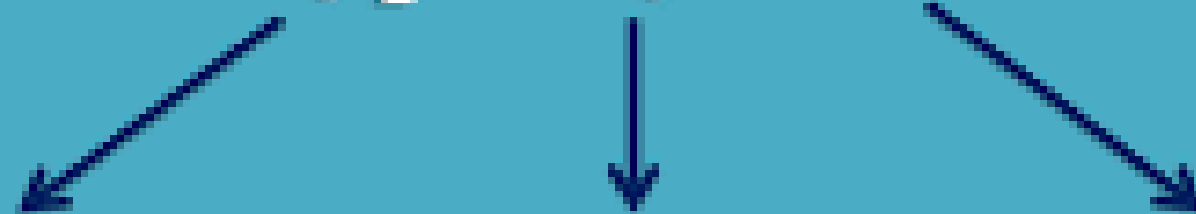
Beta 2

- Skin
- Blood vessels (Heart , liver , sk muscles)
- Smooth muscle (Lung ,uterus , eye)
- Brain

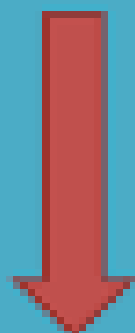
Beta 3

Lipocytes

β_1 receptors

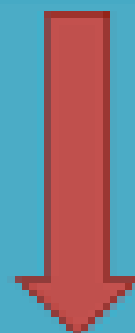


Kidney



Renin release

Heart



Rate
Force
Automaticity
Cardiac output

Adipose tissue



Lipolysis

β_2 receptors

Decreases keratinocytes proliferation

Smooth muscle

Blood vessels

Liver

Relaxation

Vasodilatation

Glycogenolysis

Eye
Bronchioles
Bladder
Uterus
GI smooth muscle

Blood vessels supplying

- Skeletal muscle
- Liver
- Heart

1. β 1 selective or non selective

First Generation (non-selective)

- Propranolol
- Timolol
- Sotalol
- Pindolol
- Nadolol

Second generation (Beta 1 selective)

- Metoprolol
- Atenolol
- Acebutolol
- Bisoprolol
- Esmolol

• **Nebivolol**

Selective types usually occur in first letters of alphabetic to M with exception Nadolol

Q/ There is no selective B2- blockers, explain why?

Advantages of cardio selective B1 Blockers

1. Less bronchospasm
2. Less effect on diabetes & hyperlipidemia
3. Less incidence of cold extremities (not precipitate Raynaud's disease & patient with peripheral vascular disease)
4. Less aggravating of psoriasis

Disadvantages of selective B1 blockers

1. Not effective in essential tremors
2. Not effective for anxiety

Advantages of non selective B Blockers

**Non-selective
 β blockers**

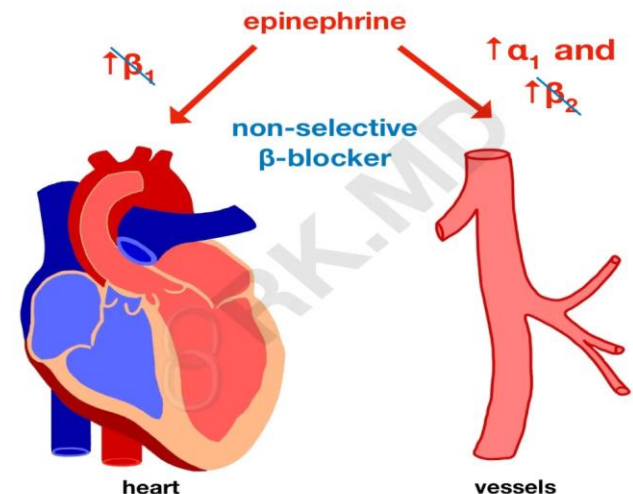
(More preferred)



Anxiety
Essential tremor

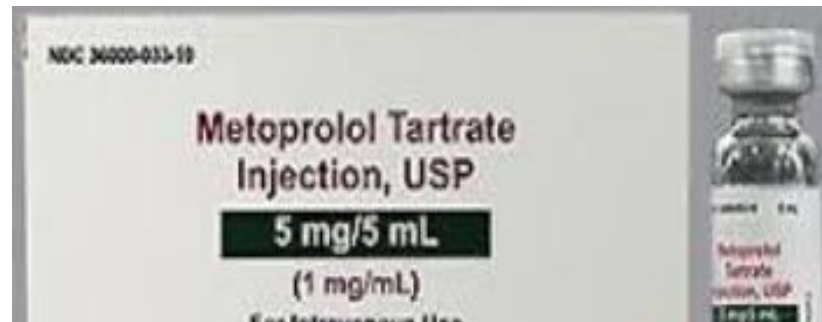
Disadvantages of non- selective BB

- Bad metabolic effects (reduction in the muscle lipoprotein lipase enzyme, which is involved in lipid metabolism.)
- More bronchospasm
- CNS (night mares)
- Cold extremities
- Fatigue
- Aggravates psoriasis



Pharmacokinetics

- All beta blockers well absorbed from GIT.
- They undergo first pass effect in liver** { decreases their levels} which may account 90% in lipid soluble types (i.e 10% reach to systemic circulation)



Also, beta blockers can be classified into

- 1) Lipophilic BB (**Propranolol**) : good absorption and have CNS effect but undergo extensive first pass effect so shorter duration of action (**liver metabolism**)
- 2) Hydrophilic (**Atenolol**) less absorption and less CNS effect ; less first pass effect , so it had long duration of action (**renal excretion**)

Pharmacological Actions:

1. Heart: a) contain B1&B2

Sympathetic Stimulation



Beta -1 receptors on myocardium



Myocardial contractility
Heart Rate
Cardiac output
Cardiac work
Oxygen consumption



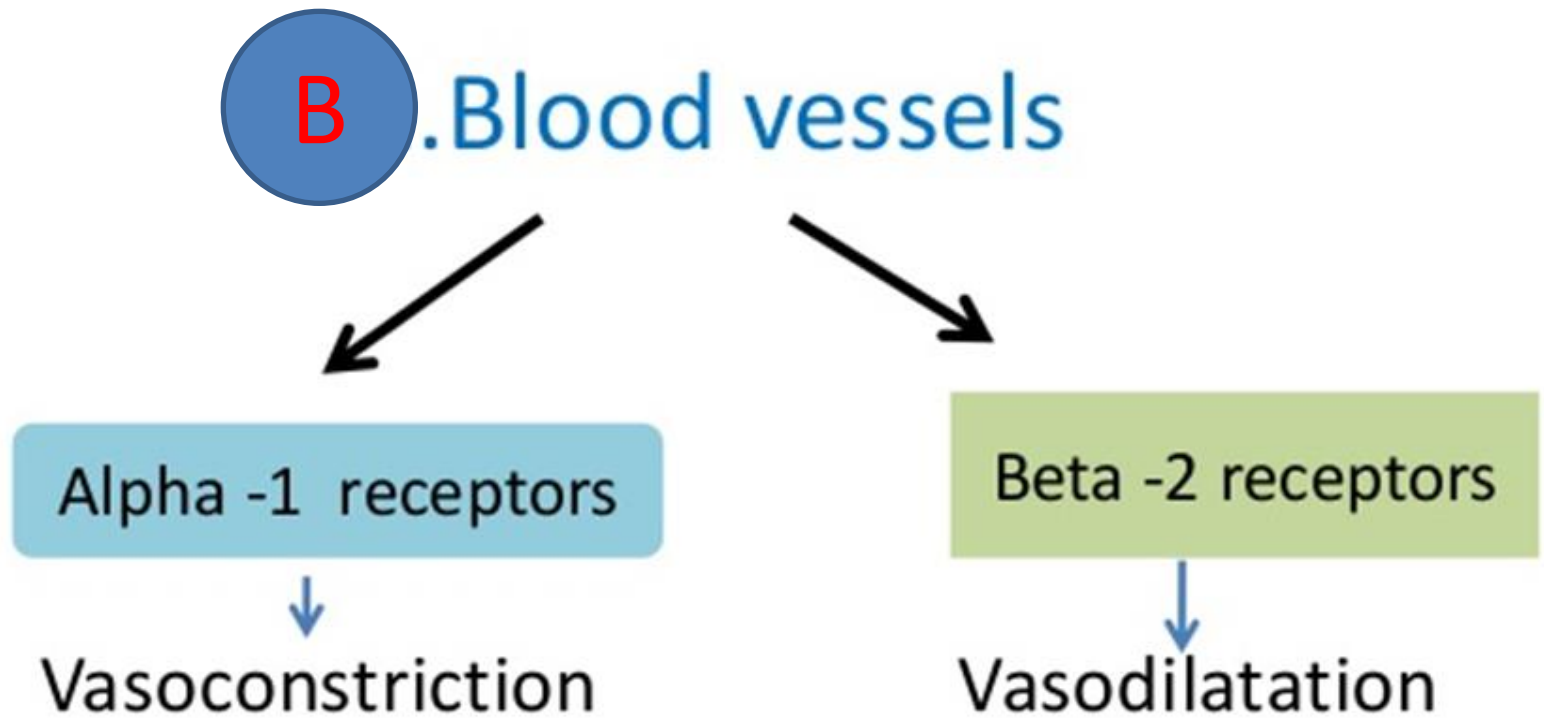
Slow cardiac conduction

Beta -2
Coronary
vasodilatation

Beta Blockers



Coronary
vasoconstriction



Non selective blocking B₁& B₂ will prevent B₂ mediated vasodilatation { this causes **vasoconstriction** is due to alpha effect } ➡ **Cold extremities**

c. Blood pressure :

BP will reduce by the following mechanisms:

- 1) Decrease COP
- 2) Decrease rennin from kidney
- 3) Reduce central sympathetic outflow
- 4) Some of BB can causes vasodilator action through alpha blocking activity or generation of NO

2

Respiratory tract

- Beta -2 receptors → bronchi → bronchodilation
- Beta blockers → broncho constriction
- Asthmatics - severe attack may be precipitated



Contraindicated
in Asthma

3) Eye :

contain B1 & B2 in ciliary body that mediate production of aqueous humor , so **beta blockers reduces IOP**



4) **CNS** : in Brain B- receptors responsible for alertness and mood , so lipid soluble BB causes **apathy** and **depression**, and **night mares** and **vivid dreams** (clear & detailed dreams)

5) **Sk m**: B2 Receptors mediate vasodilatation and tremor , so BB causes **fatigue** and **reduces tremor**.

6. Skin

Beta 2-adrenergic stimulates proteins responsible for the inhibition of keratinocyte proliferation .

So , non selective B blocker (block B2) may **trigger** or **aggravate** psoriasis



Clinical uses of B blockers

1) HT: by 4 mechanism

- All BB are effective in treatment of HT.

2) IHD :

A. Stable & unstable angina:

In **classical angina** there is atherosclerosis that causes narrowing lumen of arteries with subsequent reduced blood flow so this patient suffer chest pain esp during effort .

Using BB in this patient is very useful because:

- 1) BB reduces cardiac work
- 2) BB reduces O₂ demand

B. Myocardial infarction

1. Limit infarct size by reducing oxygen consumption
2. Prevents re- infarction
3. Decrease arrhythmias including ventricular fibrillation
4. Secondary prophylaxis of MI (use for at least 2 yr)

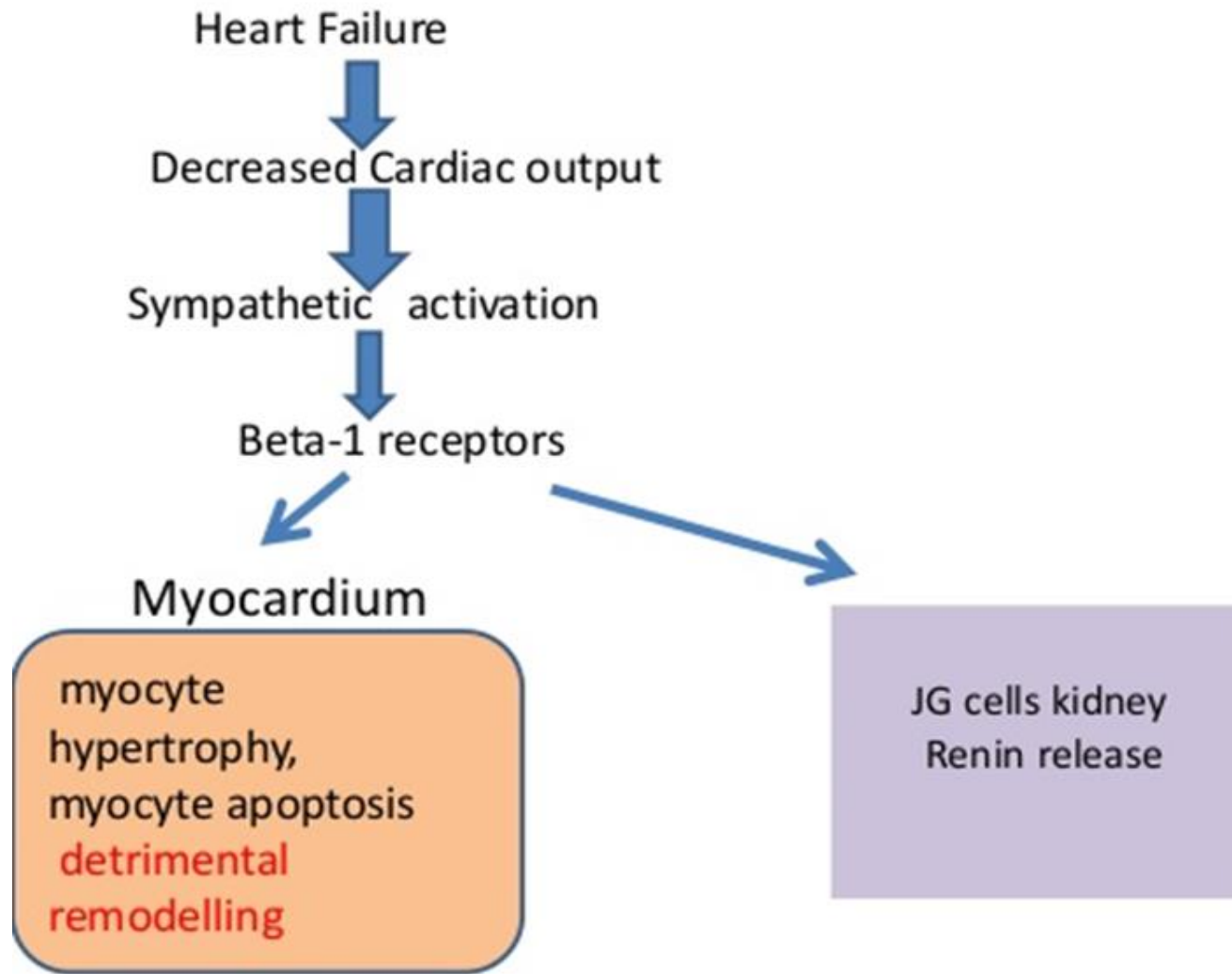
As a consequence, = Decrease subsequent mortality by 20%

Ex : **Metoprolol**

- Within 4-6 hrs Metoprolol- 5 mg i.v every 5 mins – 3 doses
- Metoprolol 25–50 mg orally every 6 h



3. Heart failure :



Beta blockers and heart failure

Use of beta blockers for patients with **unstable acute heart failure** , can cause bradycardia , hypotension , acute pulmonary edema ,cardiogenic shock .

However , **Carvedilol** , **bisoprolol** , **nebivolol** and **Metoprolol** can be used safely patients with **stable heart failure** ; but , should we have two conditions :

1. Patient should be stable (no , dyspnea , orthopnea , edema, hypotension , pulmonary congestion)
2. Should be started in lower doses and gradually increased as following

Carvedilol tab 3.12mg 1x2 for 2 weeks , then 6.25 1x2 for 2 weeks , then 12.5 mg 1x2 for 2weeks , then 25mg 1x2

4) Tachycardia (use BB - metoprolol)

- Stress induced tachycardia
- Cardiac diseases : heart failure , Atrial fibrillation , SVT
- Diabetic cardiac neuropathy
- Drugs overdose : Adrenergics , anticholinergics , stimulants , caffeine , nicotine , cocaine
- Some medical conditions : hyperthyroidism

Tachycardia (BB are contraindicated)

- Normal response to (exercise , pain)
- Medical conditions : anemia , respiratory distress , pulmonary embolism , sepsis , hypotension , hypoglycemia

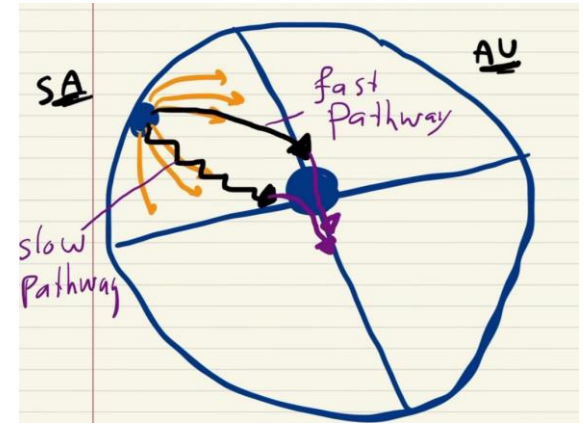
Note : it should be treated the underlying cause of tachycardia

5) Atrioventricular Nodal Reentrant Tachycardia (AVNRT):

It is called SVT (it is very common cardiac condition)

Pathophysiology :

- This is normal condition



- However , when fast pathway is blocked this lead prohibited electricity downward , while slow pathway generate circus

So , it is called slow – fast pathway
(typical & common)

In SVT where the electrical circuit (single focus) is located within the atria or AV node itself fires repeatedly at a rapid rate, causing a fast heart rhythm

Signs & symptoms:

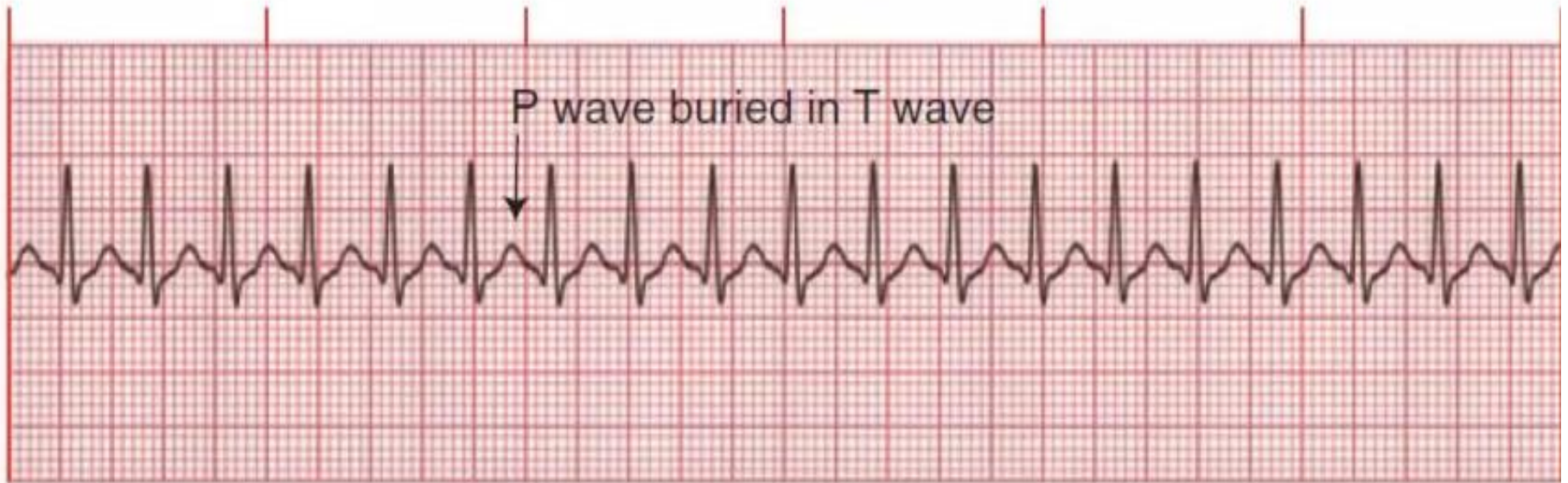
- Mild SVT is asymptomatic
- Palpitation
- Dizziness
- Chest pain
- SOB
- Sweating
- Syncope
- Polyurea (contraction → stretching in cardiac muscles → release Atrial natriuretic peptide (ANP) → stimulate urination to decreases volume

Risk Factors

- Inherited Conditions.
- Structural Abnormalities.
- Coronary Artery Disease.
- COPD.
- Pulmonary Embolism.
- Hyperthyroidism.
- Alcoholism.

Supraventricular Tachycardia (SVT)

- This arrhythmia has such a fast rate that the P waves may not be seen.

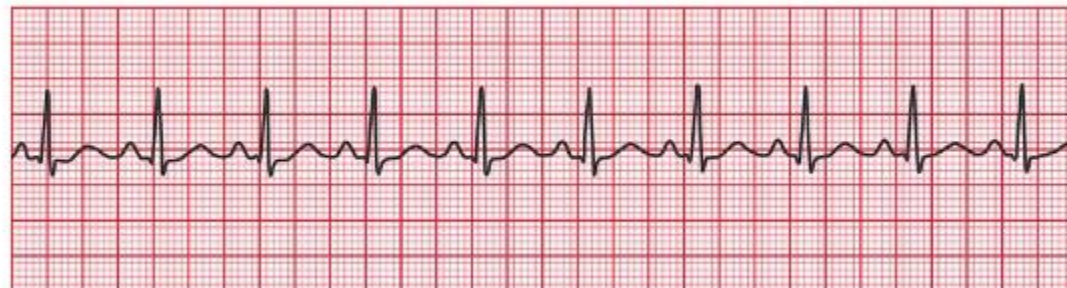


Rate: 150–250 bpm

Rhythm: Regular

P Waves: Frequently buried in preceding T waves and difficult to see

Normal heart rhythm

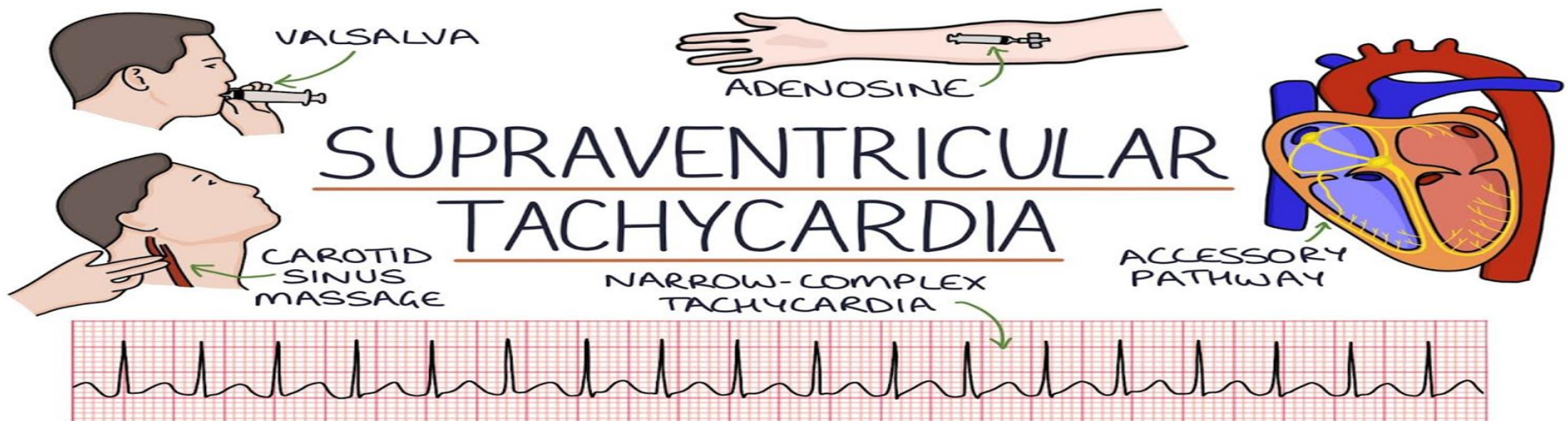


Treatment of SVT

1. Unstable patient (hypotension , acute heart failure , unconscious , severe ischemic chest pain) →→ synchronized DC shock (start with 70 J)

2. Stable patient

- vagal nerve stimulation (Valsalva maneuver , modified Valsalva maneuver , carotid massage , cold water ,cough reflex)
- Adenosine rapid IV 6mg (should be not asthmatic)
- Calcium channel blockers (verapamil iv)
- B blockers (Metoprolol iv)



6) Hypertrophic obstructive cardiomyopathy: HOCM

cardiac anomaly occur in young group (incidence 1 per 1000)

- **Feature** : thickening of inter-ventricular septum (normal thickness is max. 12mm) while in this condition may reaches 17mm , by this defect the aorta will be physically narrowed , so blood ejection is interrupted by this narrow lumen .
- **Symptoms** : shortness of breath, chest pain, and dizziness.
- **Prognosis** : Untreated cases may cause sudden death especially in athletes

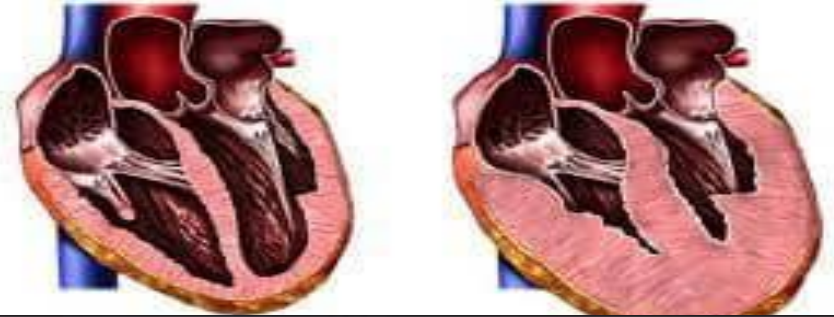
Treatment : BB because it produce bradycardia so blood ejection through aorta not congested.

Severe symptoms → septal reduction surgery

HCM is frequently asymptomatic until sudden cardiac death, and for this reason some suggest routinely screening certain populations for this disease.

HOCM :

Increase intraventricular septum thickness.



M Mode measurements values (in mm)

Aorta (<35mm)	33	LVIDd (32-52)	43
LA (<40mm)	36	LVPWd (6-11)	13
RV (<25 mm)	15	LVIDs (20-35)	36
IVSd (6-11mm)	17	LVEF (55%-70%)	30%

Valves morphology and function:

Valve	Appearance	Regurgitation	Stenosis
Mitral	Normal	0/4	NIL
Tricuspid	Normal	0/4	NIL
Aortic	Normal	0/4	NIL
Pulmonary	Normal	0/4	NIL

Myocardium and ventricular functions

Regional wall motion abnormality	Severe general wall hypokinesia	LV diastolic function	Grade-III DD
LV systolic function	Severe dysfunction	RV function	Normal TAPSE- 22 mm

Final Impression:

- Asymmetric septal hypertrophy.
- Grade-III diastolic dysfunction.
- Hypertrophic cardiomyopathy severe LV systolic dysfunction.

- Notable cases

After the death of Marc- Foé of Cameroon, his autopsy revealed HCM



- "Miki" Fehér, a Hungarian
- football player who died during a match HCM

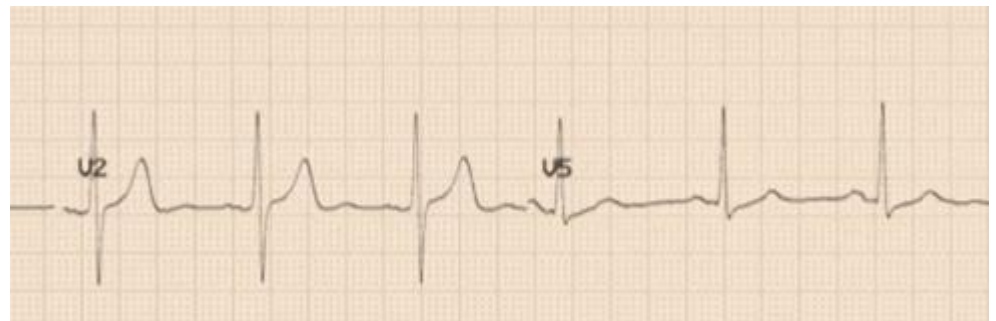
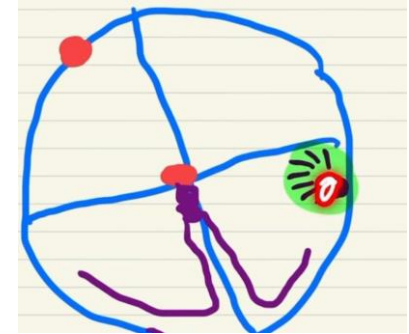


7) Premature ventricular ectopic (PVC)

- A premature ventricular complex (PVC) is a premature beat arising from an **ectopic focus** within the ventricles.

ECG finding :

- Wide QRS
- Premature wave
- Post ectopic wide distance
- No P wave



Causes

- Anxiety
- Sympathomimetics
- Excess caffeine
- Hypokalaemia
- Hypomagnesaemia
- Digoxin toxicity
- Myocardial ischemia

Complications of PVC

- Frequent PVCs might increase the risk of developing arrhythmias or cardiomyopathy .

Treatment :

- lifestyle modification

- **Beta blockers** or **calcium channels blockers** (verapamil) or **sodium channels blockers** (flecainide)



Non cardiac uses of beta blockers

Non cardiac uses of beta blockers

1) Hyperthyroidism

In hyperthyroidism , T3 & T4 stimulates cardiac B1 (causing tachycardia) and B2 in periphery causing (tremor) and central effect causing sleep disorders.

Role of BB :

- 1) Reduces sympathetic over activity
- 2) BB decrease peripheral conversion of T4 to active form T3

Note : we preferred use nonselective type in hyperthyroidism , why?

Box 5: Hyperthyroidism signs and symptoms

Common signs and symptoms of hyperthyroidism include:

- Tremor
- Tachycardia
- Warm, moist skin
- Weight loss and muscle weakness
- Agitation
- Sweating and heat intolerance
- Goitre
- Hunger and thirst
- Exophthalmos (protrusion of the eyeballs in their sockets)
- Atrial fibrillation
- Anorexia
- Diarrhoea



Atrial Fibrillation (AF)



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β blockers given -

- (i) with carbimazole or radioiodine
- (ii) with iodide preoperatively
- (iii) Thyroid storm (thyrotoxic crisis): **emergency**

Propranolol- 1-2 mg slow i.v. → 40-80 mg orally



Case 1 A 46 yr old female presented with tremor , palpitation , wt loss , heat intolerance , hair loss and exophthalmos

Lab data showed below

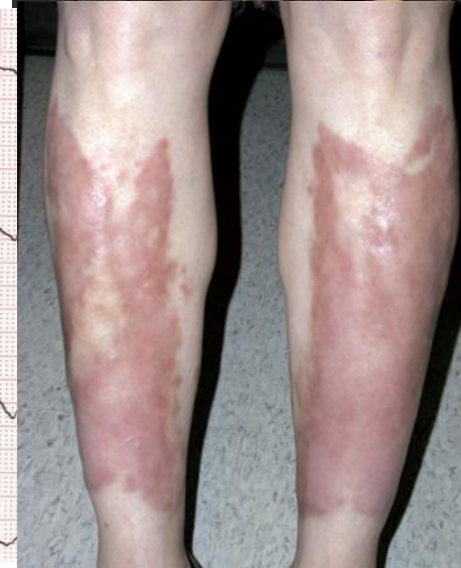
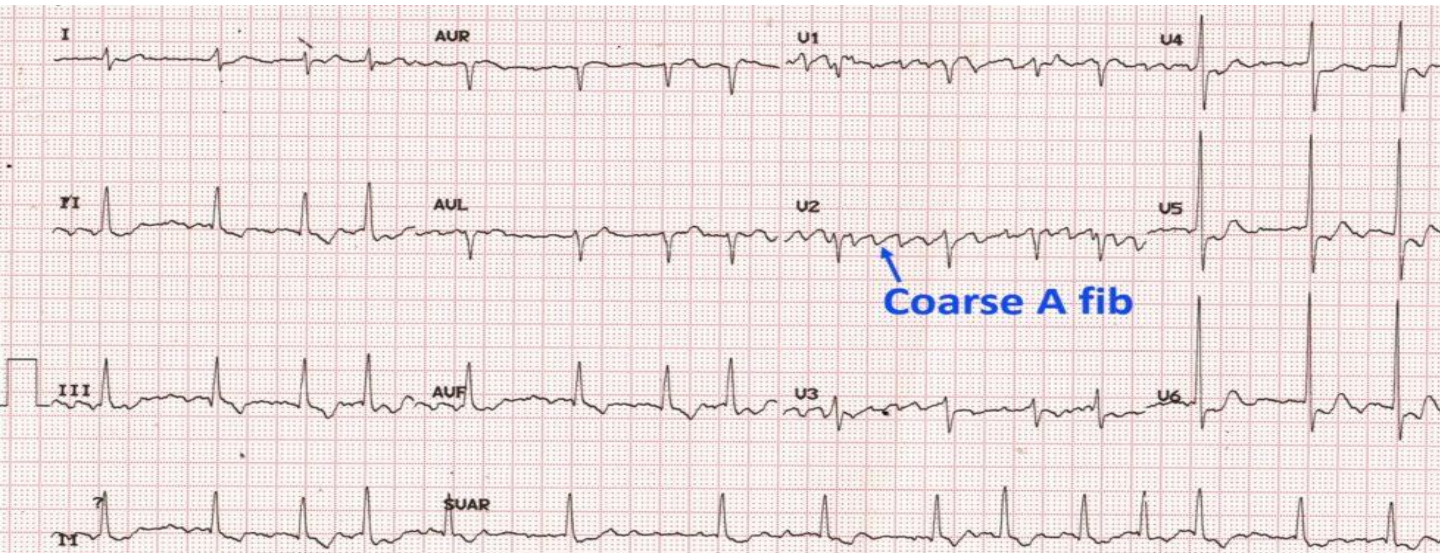
Diagnosis & treatment ?



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THYROID PANEL RESULT

TEST	RESULT	UNIT	NORMAL RANGE
T3	8.99	nmol/L	1.3 - 3.1
T4	237.73	nmol/L	66 - 181
TSH	<0.1	mIU/L	0.3 - 4.2



Answer case 1

1. **ECG finding** : atrial fibrillation (non valvular)
2. **Lab data & clinical finding** : hyperthyroidism (graves disease)
3. **Clinical finding induced by hyperthyroidism are** :

- Pretibial myxedema
- Hair loss
- Palpitation
- Tremor
- WT loss
- Nervousness
- Heat intolerance

4. Treatment :

- AF : Metoprolol iv + Anticoagulant (**Rivaroxban** tab 20mg/d)
- Hyperthyroidism : carbimazole tab 2x3 + propranolol tab
- Autoimmune (graves disease) : prednisolone 1mg/kg
- Pretibial myxedema : topical cortisone (clobetasol under occlusion)



Rx



2) Glaucoma

Primary open angle glaucoma

POAG , also referred to as chronic simple glaucoma is generally a bilateral, but not always symmetrical disease, characterized by:

- Adult onset
- IOP>21 mmHg
- An open angle of normal appearance
- Characteristic optic disc cupping
- Visual field loss

Risk factors

- Increased IOP
- Age > 50
- Family history
- DM
- Hyperthyroidism
- Smoke
- Steroid (systemic)

Timolol most commonly used eye drop in the treatment of glaucoma , why ?



Because they are most lipophilic beta blockers

- Ciliary epithelium – β -2 receptors
-increases aqueous secretion
- Their blockade reduces Aqueous secretion
- Reduces Intra- ocular pressure

3) Portal hypertension & Esophageal varicocele (liver cirrhosis)



Esophageal varices are abnormal, enlarged veins in esophagus.

Esophageal varices develop when normal blood flow to the liver is blocked by a clot or scar tissue in the liver , so blood flows into smaller blood vessels that aren't designed to carry large volumes of blood. The vessels can leak blood or even rupture, causing life-threatening bleeding.

Endoscopic features



Figure 1 Large esophageal varices at EGD.

Treatment of esophageal varicocele

Rx

- liver transplantation
- symptomatically improved by B blockers that reduces COP , so intestinal blood will decrease so that reduce blood shunt and congestion
- Endoscopic Variceal Ligation
- Surgery

4. Migraine

The **Migraine** headache is unilateral pain (affecting one half of the head) and pulsating in nature, lasting from 4 to 72 hours; symptoms include nausea, vomiting, increased sensitivity to light, increased sensitivity to sound; the symptoms are generally aggravated by routine activity.

Triggers

- Stresses

- Diet** {cheese, Alcohol, Chocolate, Caffeine, onion, Bananas}

- Hormonal changes:** Menstrual migraine

- Climate changes

- Vasodilators drugs

Diagnosis of migraine :

The mnemonic POUNDing (Pulsating, duration of 4–72 hOurs, Unilateral, Nausea, Disabling) can help diagnose migraine. .

Also, migraine may be associated with

1) photophobia and/or phonophobia.

2) Sensory hallucination

3) Visual hallucination

4) De -javue



Treatment (acute attacks)

1. Eliminating triggers
2. Sleep regulation
3. Abortive therapy (acute attacks) :
 - **NSAIDs** (ibuprofen + paracetamol) = Megafin
 - **Triptan** : 5-HT receptor agonist drugs (Vasoconstriction)



Prophylaxis (in severe recurrent attacks)

Propranolol tab 40mg -80mg/d

Most effective drug

It has been found to be effective as preventive medications , reducing the frequency of migraines in 70% patients .

Others

- **BOTOX**
- **TCA (Amitriptyline 10mg /d)**
- **Pizotifen**



5) Treatment of bruxism

Bruxism, which is characterized by grinding or clenching of teeth, is a problem that affects 10 % of the population.

Symptoms such as moderate to severe headache, muscle pain, TMJ dysfunction, and tooth damage .

Treatment

- Psychological support
- Dental guard
- Propranolol tab 40mg /d
- BOTOX .



Other dental uses of BB

1. Reduce dental anxiety symptoms
2. Prevent stress-induced angina
3. Control tremors for better cooperation
4. Manage hyperthyroid symptoms during treatment
5. Post-epinephrine tachycardia

6) Treatment of anxiety , stress

- Propranolol tab 40mg /d



7) Essential tremor

is involuntary , rhythmic & bilateral movement , often affecting the hands , head , or voice increased with movement

Causes

- Genetics
- Idiopathic

Triggers : stress , fatigue & caffeine

Treatment

- BB (Propranolol 20- 60mg /d)
- Primidone
- Topiramate



Note: Alcohol (intermittently decreases ET)

8) Infantile hemangioma : A benign tumor of endothelial cells that appears in early infancy, grows rapidly, then involutes slowly.

Three phases:

1. Proliferative phase (rapid growth)

2. Plateau phase

3. Involution phase

1. 50% gone by age **5yr**

2. 70% by **7yr**

3. 90% by **9–10yr**



Fig. 3: Intra oral view showing bluish purple

Treatment

Beta-blockers: propranolol has anti-angiogenic effects, can cause rapid involution of hemangiomas.

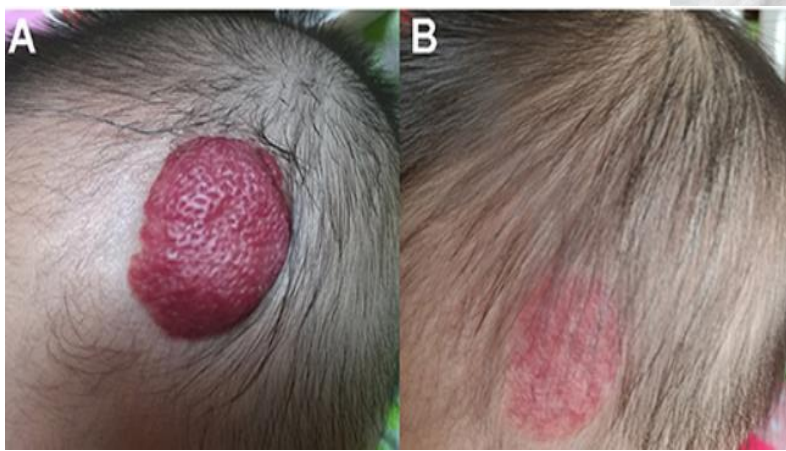
Most infants reported have been treated with propranolol at a dose of **2 mg/kg/d in 2 divided doses**.

Duration of therapy varies from 2-10 months.

Note : topical B blockers also effective such as **timolol drop** or formulation of **propranolol as 1% ointment**



skin Hemangioma



Side effects OF beta blockers

- 1) **Fatigue** (because reducing COP (B1), blood flow into muscles (B2).
- 2) **Bronchoconstriction** (due to blocking B2 in lung ; even selective type is contraindication in asthmatic patient).
- 3) **Bradycardia** (so it is contraindication in heart block).
- 4) **Depression** { central B2 blocking).
- 6) **Promote angiogenesis** , so they are contraindicated in psoriatic patients
- 7) **Mask symptoms of hypoglycemia** in diabetic patients (tremor & sweating)

B blockers & DM

Advantages : some diabetic patients have neuropathy as complication { one of neuropathy damage parasympathetic nerve supplying heart causing tachycardia }

Disadvantages :

a. in DM , beta blockers mask symptoms of hypoglycemia such as tremor , sweating , and tachycardia

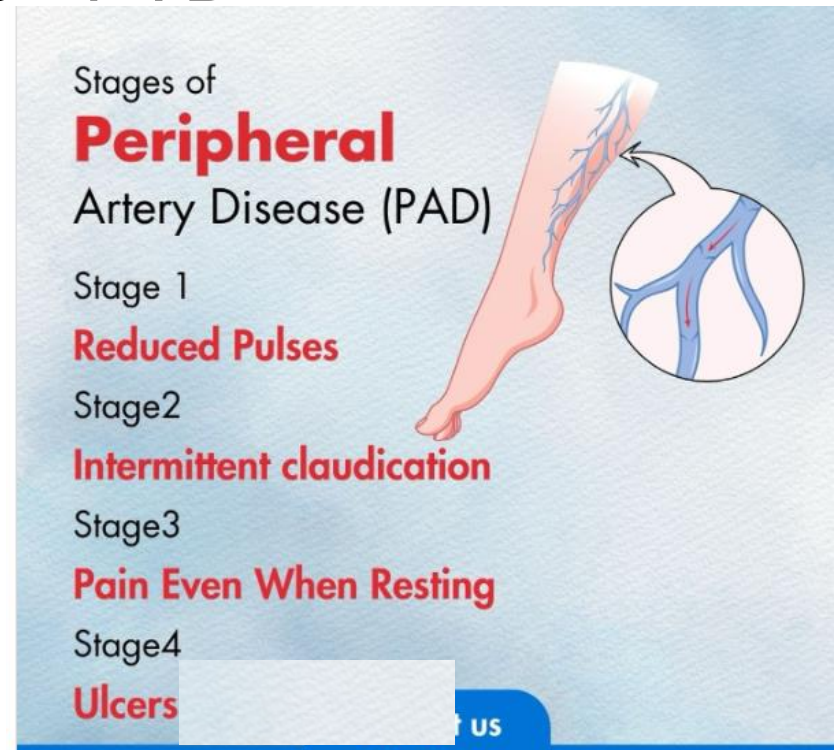
B . In DM , Beta Blockers block glycogenolysis that mediated through B2 stimulation in liver during hypoglycemia induced by drugs or to insulin therapy .

Withdrawal of Beta blockers

- Abrupt withdrawal of BB should not be done (ppt. angina attack & acute MI due to sudden ↑ sympathetic tone of heart; upregul. Of beta rec.

Contraindications

1. Asthma & COPD
2. Severe bradycardia / heart block
3. Uncompensated heart failure
4. Peripheral vascular disease - PVD



The End