

# CALCIUM CHANNEL BLOCKERS

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## CCB

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- It has been known since the late 1800s that transmembrane calcium influx is necessary for the contraction of smooth and cardiac muscle. The discovery of a calcium channel in cardiac muscle was followed by the finding of several different types of calcium channels in different tissues.
- Although the blockers currently available for clinical use in cardiovascular conditions are exclusively L-type calcium channel blockers.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	Ca <sub>v</sub> 1.1–Ca <sub>v</sub> 1.3	Cardiac, skeletal smooth muscle, neurons (Ca <sub>v</sub> 1.4 is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd <sup>2+</sup> , -aga-III A
T	Ca <sub>v</sub> 3.1–Ca <sub>v</sub> 3.3	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, mibefradil <sup>1</sup>
N	Ca <sub>v</sub> 2.2	Neurons, sperm <sup>2</sup>	Short, high threshold	Ziconotide <sup>3</sup> gabapentin <sup>4</sup> -CTX- GVIA, -aga-III A, Cd <sup>2+</sup>
P/Q	Ca <sub>v</sub> 2.1	Neurons	Long, high threshold	-CTX-MV1C, -aga-IV A

# CCB

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- They divided into three chemical classes:
- a. Diphenylalkylamines, Verapamil.
- b. Benzothiazepines, Diltiazem
- c. Dihydropyridines, Nifedipine

## Calcium channel blockers

Phenylalkylamines

Verapamil

Benzothiazepines

Diltiazem

Dihydropyridines

1st generation

Nifedipine

2nd generation

Isradipine

Nicardipine

Felodipine

3rd generation

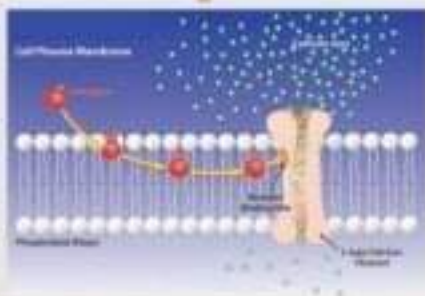
Amlodipine

## • MECHANISM OF ACTION

- Calcium enters muscle cell through special voltage sensitive calcium channel.
- Normally, L-Type of channels admit  $\text{Ca}^{+}$  and causes depolarization – excitation-contraction coupling through phosphorylation of myosin light chain – contraction of vascular smooth muscle – elevation of BP CCBs block L-Type
- These agents exert their effect by antagonists block for the inward movement of calcium by binding to the L-type channels in the heart and peripheral vasculature

### Calcium channel blockers

MOA:



## ORGAN SYSTEM EFFECTS

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- **1. Smooth muscle:** dependent on transmembrane calcium influx for normal resting tone and contractile responses.
- Vascular smooth muscles (most sensitive) relaxed by the calcium channel blockers.
- reduction in peripheral vascular resistance .
- Reduction of coronary artery spasm .

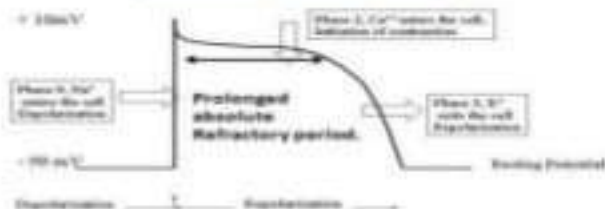


## 2. CARDIAC MUSCLE

- Normally: highly dependent on calcium influx during each action potential for normal function (plateau).
- Impulse generation in the sinoatrial node and conduction in the atrioventricular node.

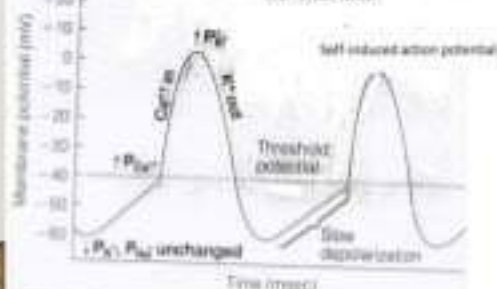
• reduce cardiac contractility, decrease CO, reduce oxygen requirement in with

### Monophasic Action Potential (Cardiac Muscle Cell)



The plateau phase of the cardiac muscle action potential – provides a longer absolute refractory period – thus disallowing cardiac muscle action potentials from coming too close together – thus disallowing cardiac muscle tetany.

### Automaticity of the Sino Node





### *3. SKELETAL MUSCLE*

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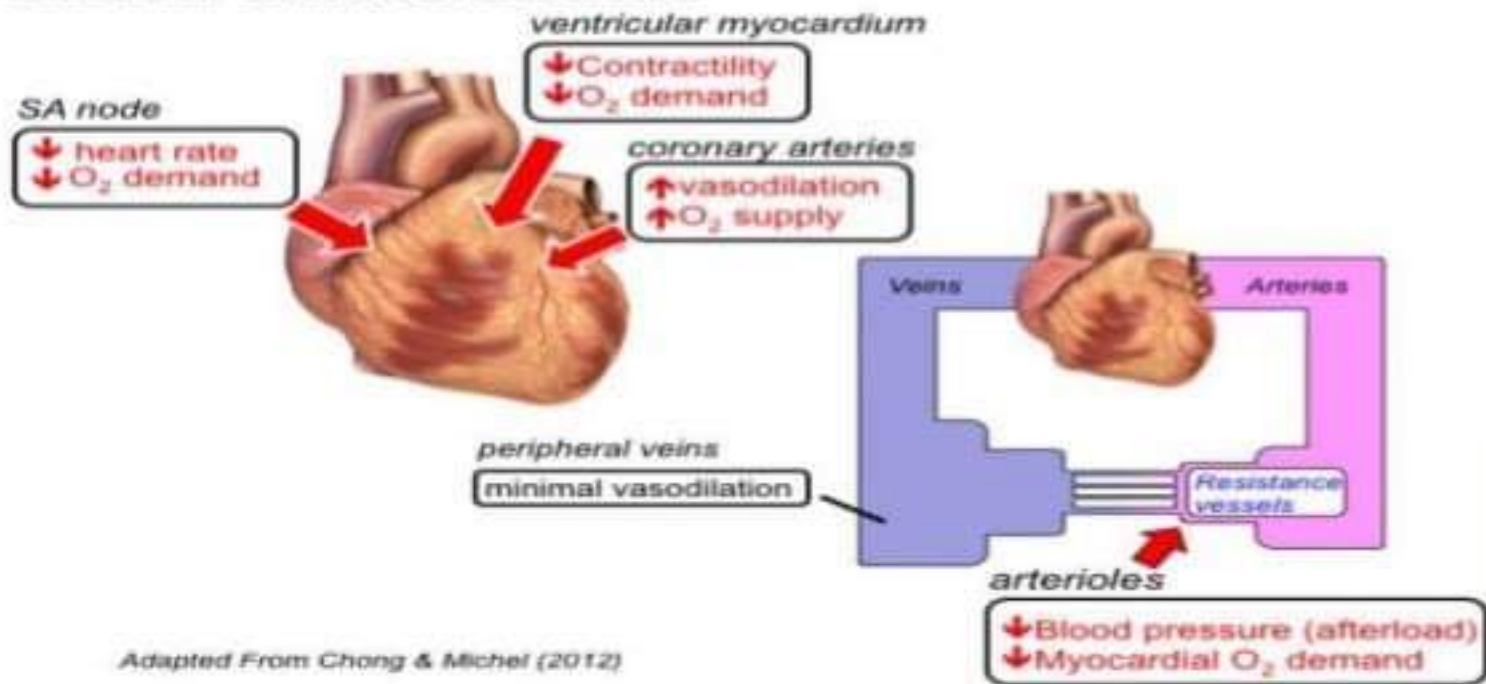
- Skeletal muscle is not depressed by the calcium channel blockers because it uses intracellular pools of calcium to support excitation-contraction coupling and does not require as much transmembrane calcium influx.

# CLINICAL EFFECTS

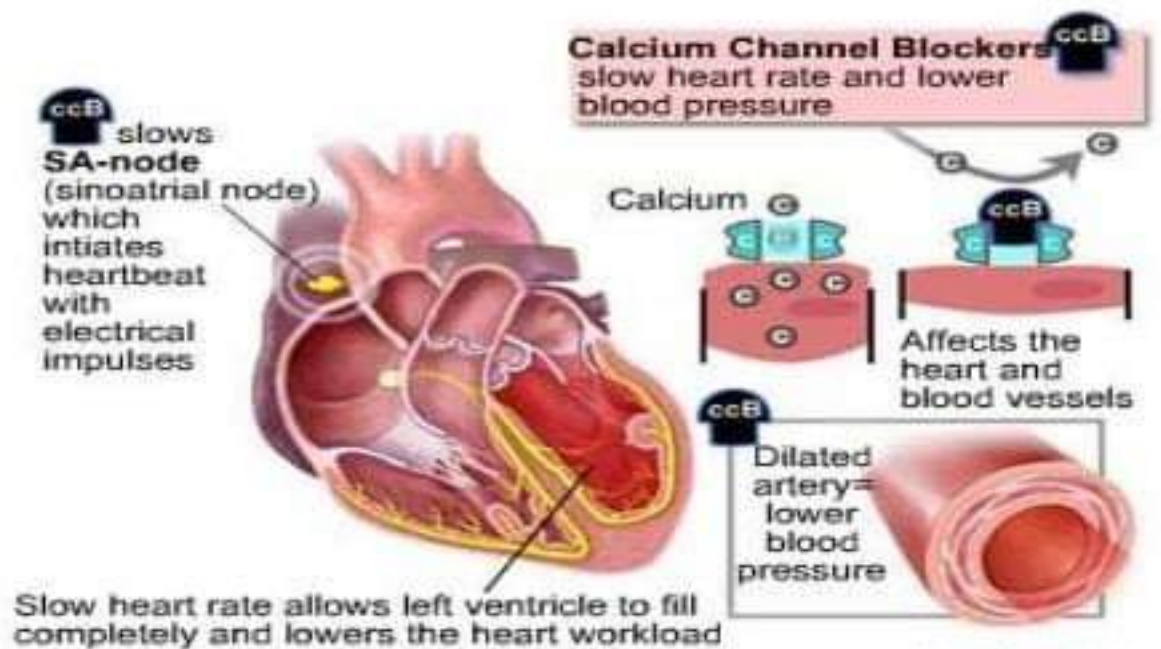
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- decrease myocardial contractile force.
- reduces myocardial oxygen requirements.
- Decrease peripheral resistance .
- Decreased heart rate with the use of verapamil or diltiazem causes a further decrease in myocardial oxygen demand.

## Calcium Channel Blockers



## Calcium Channel Blockers



	NIFEDIPINE	DILTIAZEM	VERAPAMIL
coronary arteries dilation	++	++	++
peripheral arteries dilation	++++	++	+++
negative inotropic	+	++	+++
slowing AV cond	↔	+++	++++
heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood pressure	++++	++	+++
depression of SA	↔	++	++
increase in cardiac output	++	↔	↔

# INDICATIONS

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- Angina.
- Hypertension.
- Raynaud's phenomenon. (Nifedipine is the mainstay of medical treatment).
- Supraventricular tachycardias, including atrial fibrillation.
- Ischaemic neurological deficit after subarachnoid haemorrhage.
- Delay of preterm labour(prevent premature labour has been with nifedipine)
- Prophylaxis for cluster headache.



## USAGE

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- Verapamil and Diltiazem are used in arrhythmias because they have an effect on the heart. They both are not great antihypertensive drugs
- because they have negative inotropic and chronotropic effects,
- however are used in patients who have palpitations/arrhythmias and suffer from HTN since they can reduce heart rate and blood pressure simultaneously.
- Dihydropyridines: depend on **JNC-8, found in first line therapy espically in black population** have a **high efficacy** of 40 mmHg, regarding that the highest reduction in blood pressure an orally taken anti-hypertensive drug can cause is 40 mmHg.



# ADVERSE EFFECTS

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- Common adverse effects
- These can be predicted from the type of CCB and mode of action, as already illustrated. Examples include:
  - **Myocardial effects**
    - Hypotension
    - Heart failure
  - **Conduction effects**
    - Heart block
    - Arrhythmias

# ADVERSE EFFECTS

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- **Vascular smooth muscle**

- Flushing
- Oedema
- Headaches
- Rashes

- **Other effects**

- Constipation
- Rashes
- Gynaecomastia
- Photosensitivity

## ADVERSE EFFECTS

drug	Effect on heart rate	Adverse effect
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling, Gingival hyperplasia
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

## CAUTIONS AND CONTRA-INDICATIONS

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- Again, these can be predicted from the type of CCB and mode of action. Individual drug monographs need to be reviewed. Some examples include:
- Cardiovascular: shock, unstable angina, significant aortic stenosis, bradycardia, heart failure, etc.
- Avoidance of grapefruit juice with felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil. This may affect metabolism.
- Sudden withdrawal of CCBs may exacerbate angina.
- These are best considered under each individual drug.