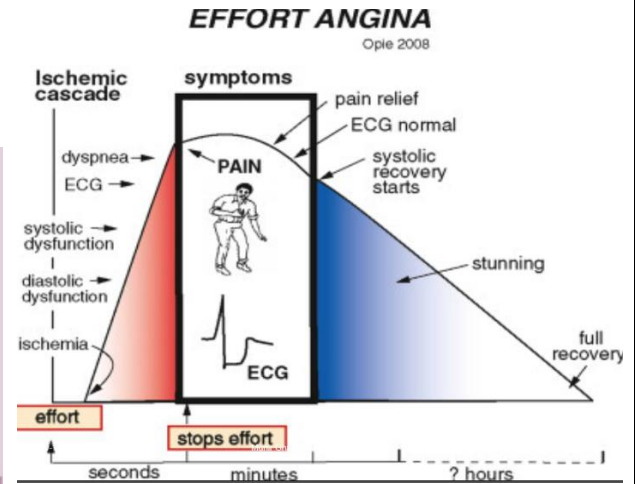
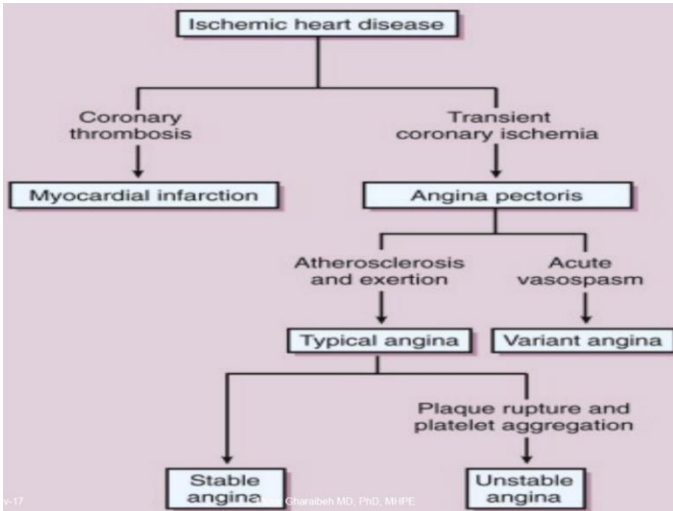


## Drug Treatment of Ischemic Heart Disease

### Categories of Ischemic Heart Disease

- Fixed "Stable", Effort Angina
- Variant Angina "Primary Angina"
- Unstable Angina
- Myocardial Infarction



### Comparison between primary & secondary angina

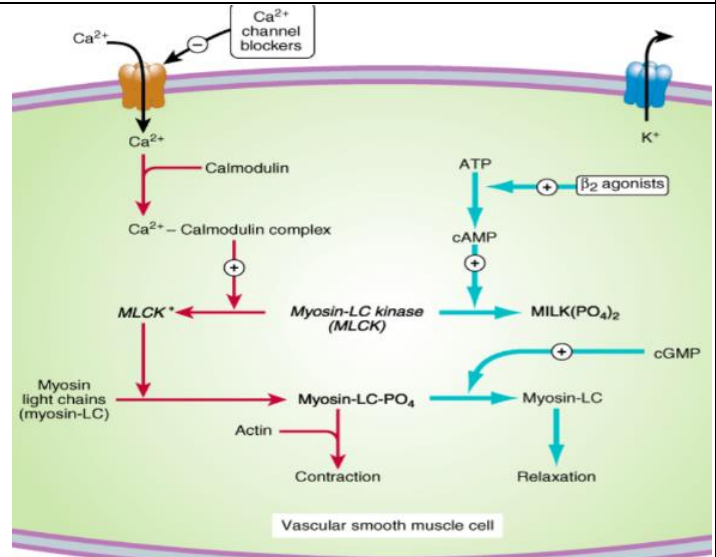
Primary	Variant (Prinzmetal's)	Angina at rest	Atypical	1957	Large vessels	Single	Vasospasm	ST elevation
Secondary	Classical	Angina of effort	Typical	1768	Small vessels	Single or multiple	Atherosclerosis	ST depression

### A condition that may happen after reperfusion

Stunning : (مشدود، مذهبول، مصعوق)  
Myocardial stunning is the reversible reduction of function of heart contraction after reperfusion not accounted for by tissue damage or reduced blood flow.

### Control of smooth muscle contraction

- Contraction is triggered by influx of calcium through L-type transmembrane calcium channels.
- Calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (MLCK\*).
- MLCK phosphorylates myosin light chains, thereby initiating the interaction of myosin with actin.
- Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK and by facilitating the expulsion of calcium from the cell.



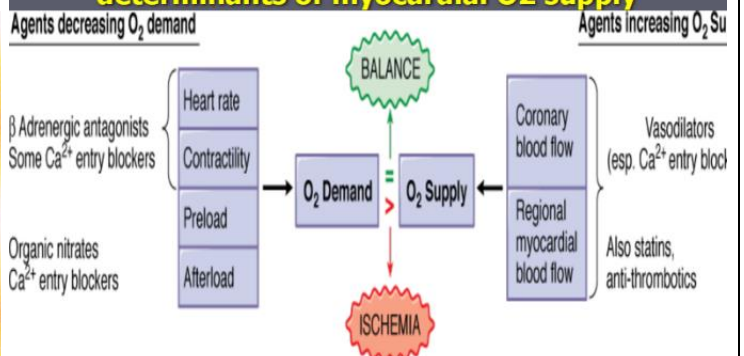
### Mechanism of IHD

Imbalance of the ratio:  
O<sub>2</sub> Supply (Coronary Blood Flow)  
O<sub>2</sub> Demand (Work of the Heart)

### Major Determinants of Myocardial Oxygen Supply and Demand

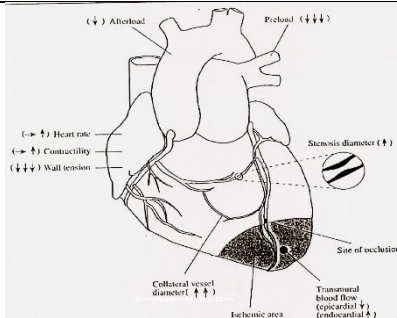
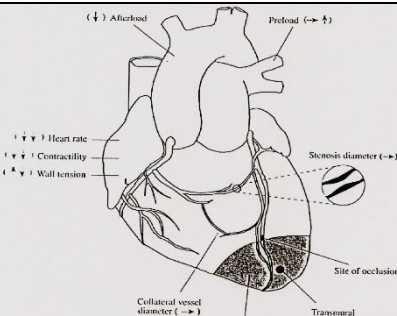
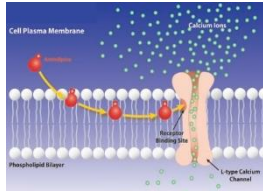
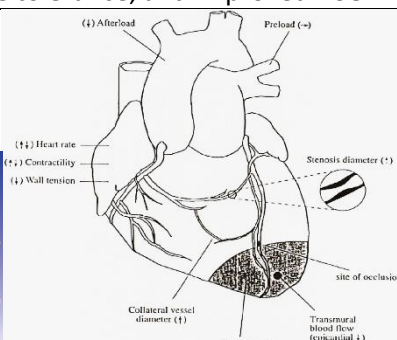
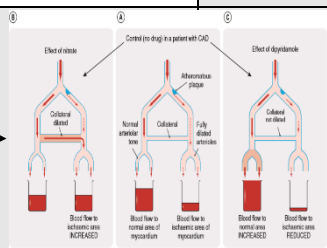
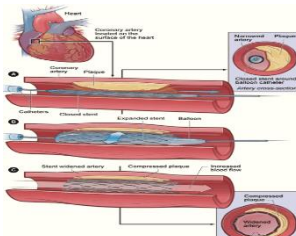
Oxygen supply	Oxygen demand
Oxygen extraction (%)	Wall tension
Coronary blood flow	Ventricular volume
Aortic diastolic pressure	Radius or heart size
Coronary arteriolar resistance	Ventricular pressure
Metabolic autoregulation	Systolic pressure (afterload)
Endocardial-epicardial flow	Diastolic pressure (preload)
Coronary collateral blood flow	Heart rate
Large coronary artery diameter	Contractility

### Pharmacological modification of the major determinants of myocardial O<sub>2</sub> supply



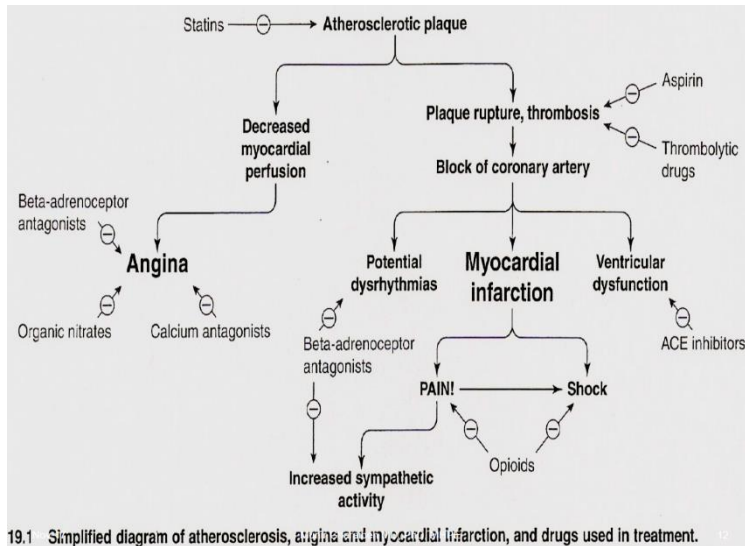
## Drugs

To read small pictures'  
details please zoom in (🔍)

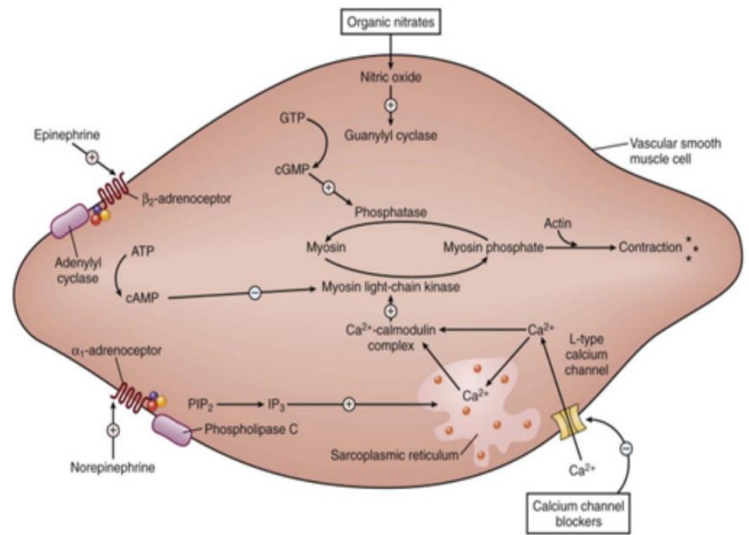
Drug	Action		Side Effects	Notes
<b>Organic Nitrates</b>  Nitroglycerine (GTN)	<ul style="list-style-type: none"><li>-Nonspecific smooth muscle relaxant.</li><li>-Action is due to release of NO, leading to activation of guanylyl cyclase.</li><li>-Action not antagonized by any known antagonist.</li></ul> <p><u>Causes general vasodilation:</u></p> <ul style="list-style-type: none"><li>*Arteriolar dilation: short lived (5-10 min)</li><li>-Decreases systemic blood pressure (afterload). This can elicit the baroreceptor reflex to cause reflex tachycardia and increased contractility, and might increase MVO2.</li><li>*Venous dilation: more intense, even with low doses, lasts for 30 minutes.</li><li>-Decreases venous return (preload) and decreases MVO2.</li></ul>		<ul style="list-style-type: none"><li>Headache.</li><li>-Hypotension and tachycardia.</li><li>-Increased intraocular and intracranial pressures.</li><li>-Methemoglobinemia.</li><li>-Tolerance: only for the arteriolar effects.</li><li>-Withdrawal: in workers in ammunition industry.</li></ul>	<ul style="list-style-type: none"><li>-Prototype, used for more than 150 years.</li><li>-Usually administered sublingually.</li><li>-Can be administered by various routes.</li><li>-Fast onset of action(1-3minutes, Peaks at 10 minutes).</li><li>-Short duration (15-30minutes).</li><li>-Reductase enzyme, in liver, breaks down the drug.</li></ul>
<b>Beta Adrenergic Blockers</b>	<ul style="list-style-type: none"><li>-Prevent actions of catecholamines, so more effective during exertion.</li><li>-Do not dilate coronary arteries, might constrict them.</li><li>-Do not increase collateral blood flow.</li><li>-Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.</li></ul>			
<b>Calcium Channel Blockers</b>	<ul style="list-style-type: none"><li>-Particularly beneficial in vasospasm.</li><li>-Can also affect platelets aggregation.</li></ul> 		<ul style="list-style-type: none"><li>-Hypotension.</li><li>-Headache, dizziness.</li><li>-Flushing.</li><li>-Peripheral edema.</li></ul> <p><u>May be dangerous in the presence of heart failure and in patients susceptible to hypotension.</u></p>	
<b>Dipyridamole</b>	<ul style="list-style-type: none"><li>-Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.</li><li>-Thought to be a good coronary dilator.</li><li>-Increases the blood flow to the normal area i.e. "Coronary Steal Phenomenon".</li><li>-Still used as an antiplatelet drug (in TIAs), but not better than aspirin.</li></ul>			
<b>Others:</b> <ul style="list-style-type: none"><li>-ACEI.</li><li>-Anticoagulants and/or Thrombolytic Therapy.</li><li>-Cholesterol Lowering Agents.</li><li>-Angioplasty</li><li>-Surgery.</li></ul>				
<b>Newer Antianginal Drugs</b> <ul style="list-style-type: none"><li>-Metabolic modulators: Ranolazine.</li><li>-Potassium channel activators: Nicorandil.</li><li>-Sulfonylureas: Glibenclamide.</li><li>-Nitric oxide donors: L- arginine.</li></ul>	<div><div><ul style="list-style-type: none"><li>-Direct bradycardic agents: Ivabradine.</li><li>-Rho-kinase inhibitors: Fasudil.</li><li>-Thiazolidinediones.</li><li>-Capsaicin.</li></ul></div><div><ul style="list-style-type: none"><li>-Vasopeptidase inhibitors.</li><li>-Amiloride.</li></ul></div></div>			



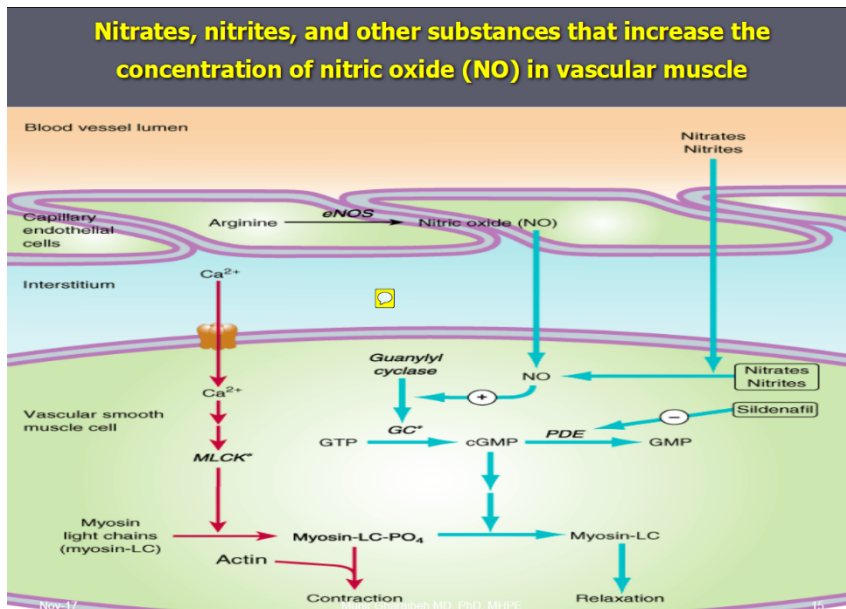
## Drugs Site of Action



19.1 Simplified diagram of atherosclerosis, angina and myocardial infarction, and drugs used in treatment.



## Organic Nitrates



### Preparations of Nitrate

#### Drug

#### Short-acting:

**Nitroglycerin, sublingual**

**Isosorbide dinitrate, sublingual**

**Amyl nitrite, inhalant**

#### Long-acting:

**Nitroglycerin, oral sustained-action**

**Nitroglycerin, 2% ointment, transdermal**

**Nitroglycerin, slow-release, buccal**

**Nitroglycerin, slow-release patch, transdermal**

**Isosorbide dinitrate, sublingual**

**Isosorbide dinitrate, oral**

**Isosorbide dinitrate, chewable oral**

#### Duration of Action

**10–30 minutes**

**10–60 minutes**

**3–5 minutes**

**6–8 hours**

**3–6 hours**

**3–6 hours**

**8–10 hours**

**1.5–2 hours**

**4–6 hours**

**2–3 hours**

**TABLE 12-2 Beneficial and deleterious effects of nitrates in the treatment of angina.**

Effect	Result
<b>Potential beneficial effects</b>	
Decreased ventricular volume	Decreased myocardial oxygen requirement
Decreased arterial pressure	
Decreased ejection time	
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
<b>Potential deleterious effects</b>	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	Increased myocardial oxygen requirement
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

## Calcium Channel Blockers

Properties of Several Recognized Voltage-Activated Calcium Channels.				
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-IIIa
T	Ca <sub>v</sub> 3.1–Ca <sub>v</sub> 3.3	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni <sup>2+</sup> , 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-IIIa, Cd <sup>2+</sup>
P/Q	Ca <sub>v</sub> 2.1	Neurons	Long, high threshold	-CTX-MVIA, -aga-IVA
R	Ca <sub>v</sub> 2.3	Neurons, sperm <sup>2</sup>	Pacemaking	SNX-482, -aga-IIIa

Calcium channel blockers		Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
<ul style="list-style-type: none"> <li>Phenylalkylamines <ul style="list-style-type: none"> <li>Verapamil</li> </ul> </li> <li>Benzothiazepines <ul style="list-style-type: none"> <li>Diltiazem</li> </ul> </li> <li>Dihydropyridines <ul style="list-style-type: none"> <li>1st generation <ul style="list-style-type: none"> <li>Nifedipine</li> </ul> </li> <li>2nd generation <ul style="list-style-type: none"> <li>Isradipine</li> <li>Nicardipine</li> </ul> </li> <li>3rd generation <ul style="list-style-type: none"> <li>Amlodipine</li> </ul> </li> </ul> </li> </ul>		<b>Dihydropyridines</b>			
		Amlodipine	65–90	30–50	Angina, hypertension
		Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
		Isradipine	15–25	8	Hypertension
		Nicardipine	35	2–4	Angina, hypertension
		Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
		Nimodipine	13	1–2	Subarachnoid hemorrhage
		Nisoldipine	< 10	6–12	Hypertension
		Nitrendipine	10–30	5–12	Investigational
		<b>Miscellaneous</b>			
		Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
		Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

## Drug Combinations

Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.			
	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	Reflex <sup>1</sup> increase	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	Increase	Non or decrease
Contractility	Reflex <sup>1</sup> increase	Decrease	Non
Ejection time	Decrease	Increase	Non