Drug Treatment of Ischemic Heart Disease

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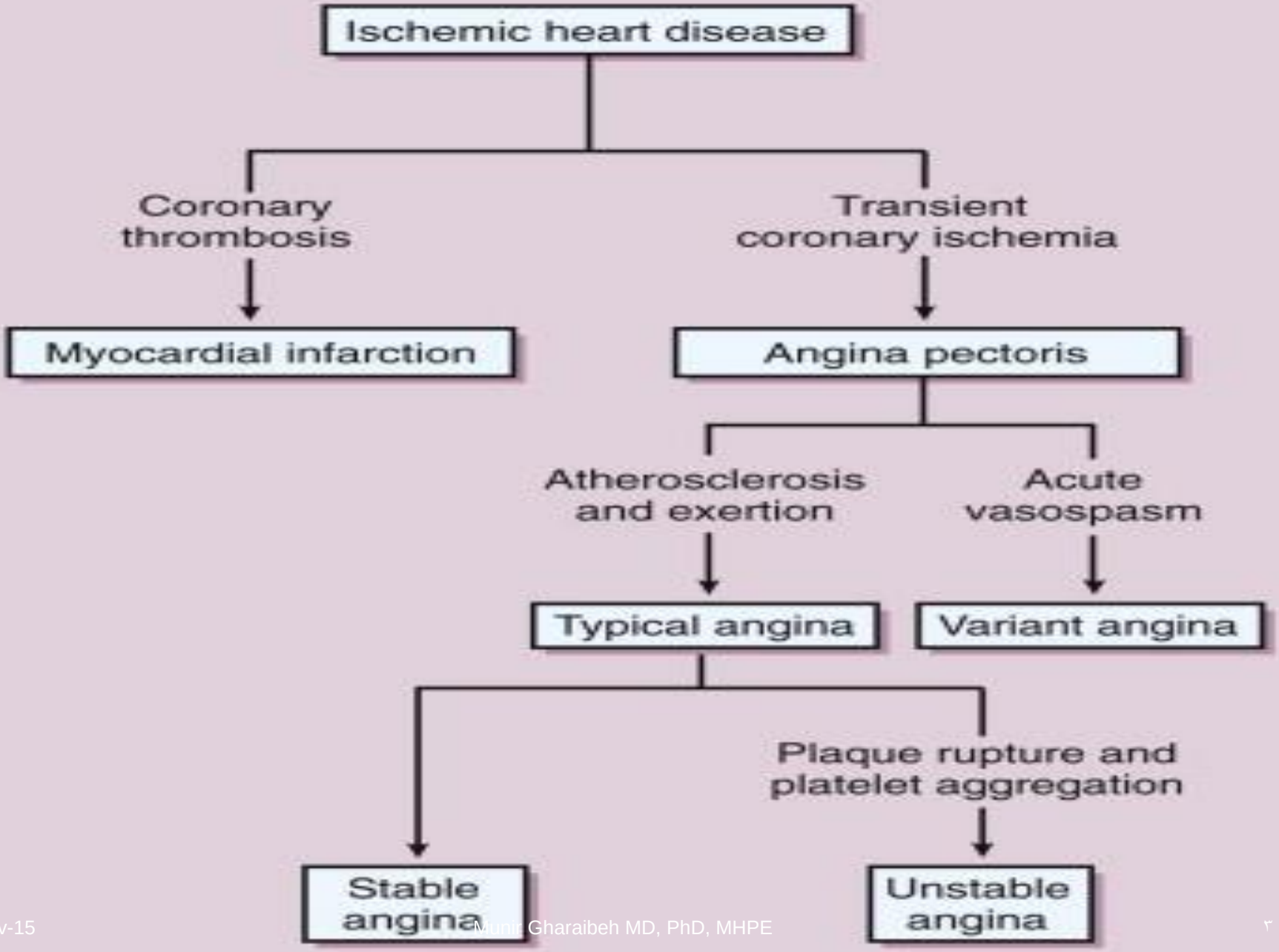
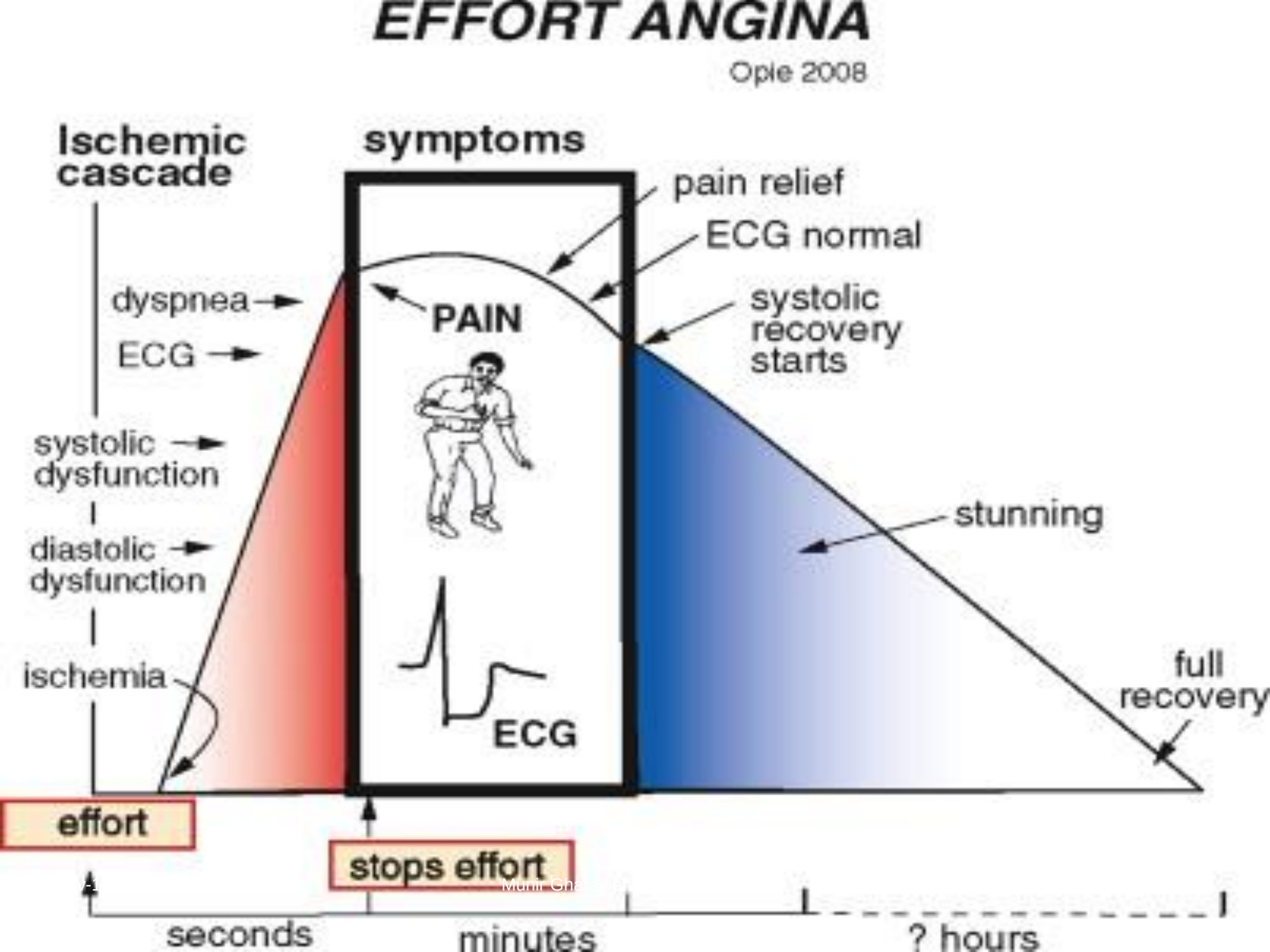
Categories of Ischemic Heart Disease

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


Ischemic heart disease
Coronary thrombosis
Transient coronary ischemia
Myocardial infarction
Angina pectoris
Atherosclerosis and exertion
Acute vasospasm
Typical angina
Variant angina
Plaque rupture and platelet aggregation
Stable angina
Unstable angina

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

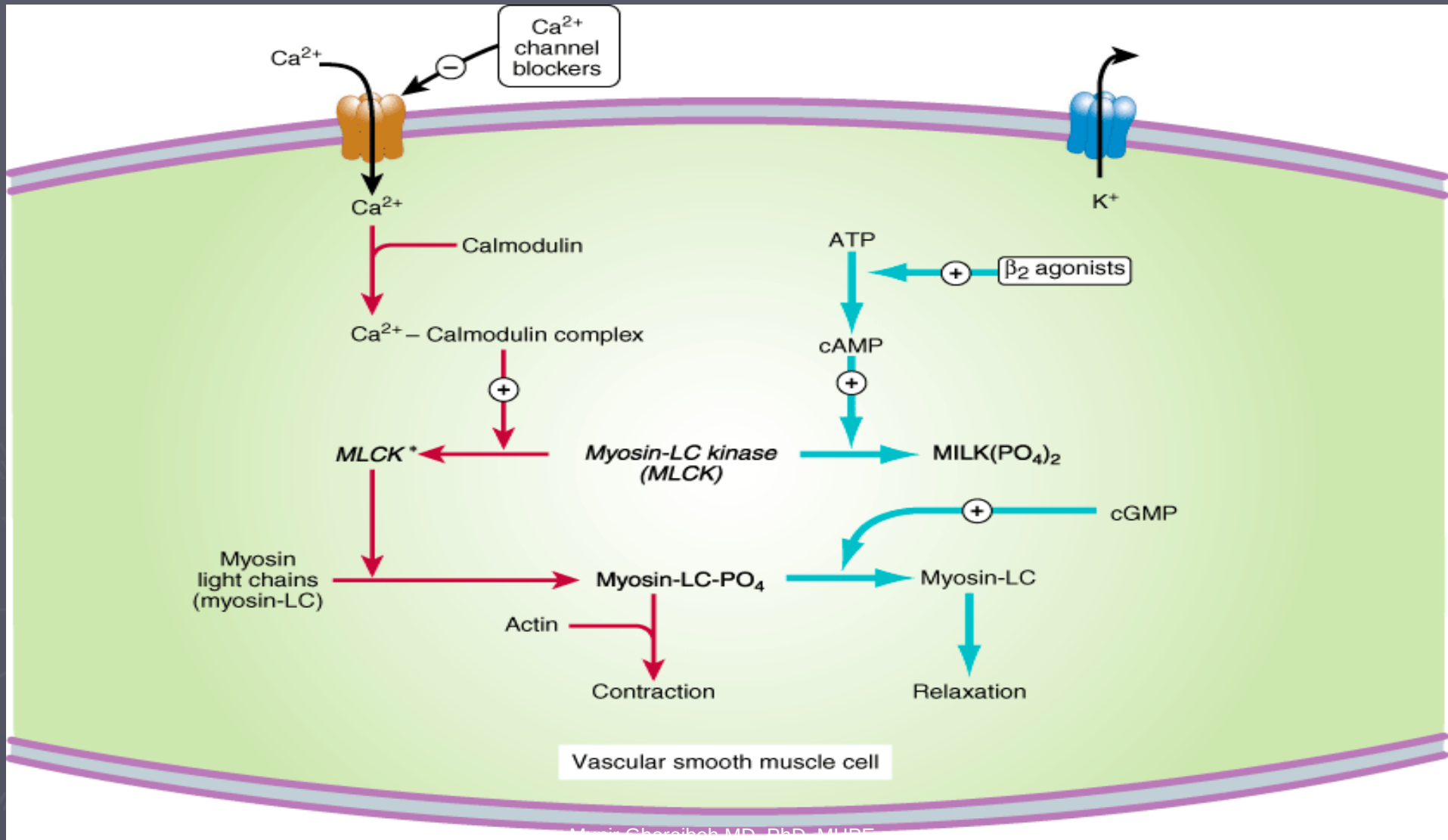

EFFORT ANGINA
Opie 2008
Ischemic cascade
symptoms
pain relief
ECG normal
dyspnea
ECG
PAIN
systolic recovery starts
systolic dysfunction
diastolic dysfunction
ischemia
stunning
full recovery
ECG
effort
stops effort
seconds
minutes
? hours

- **Stunning?(مدوخ):**
  - **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.
- The calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (*MLCK**).
- MLCK phosphorylates the 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.

Control of vascular smooth muscle contraction



Mechanism of IHD

Due to an imbalance of the ratio:

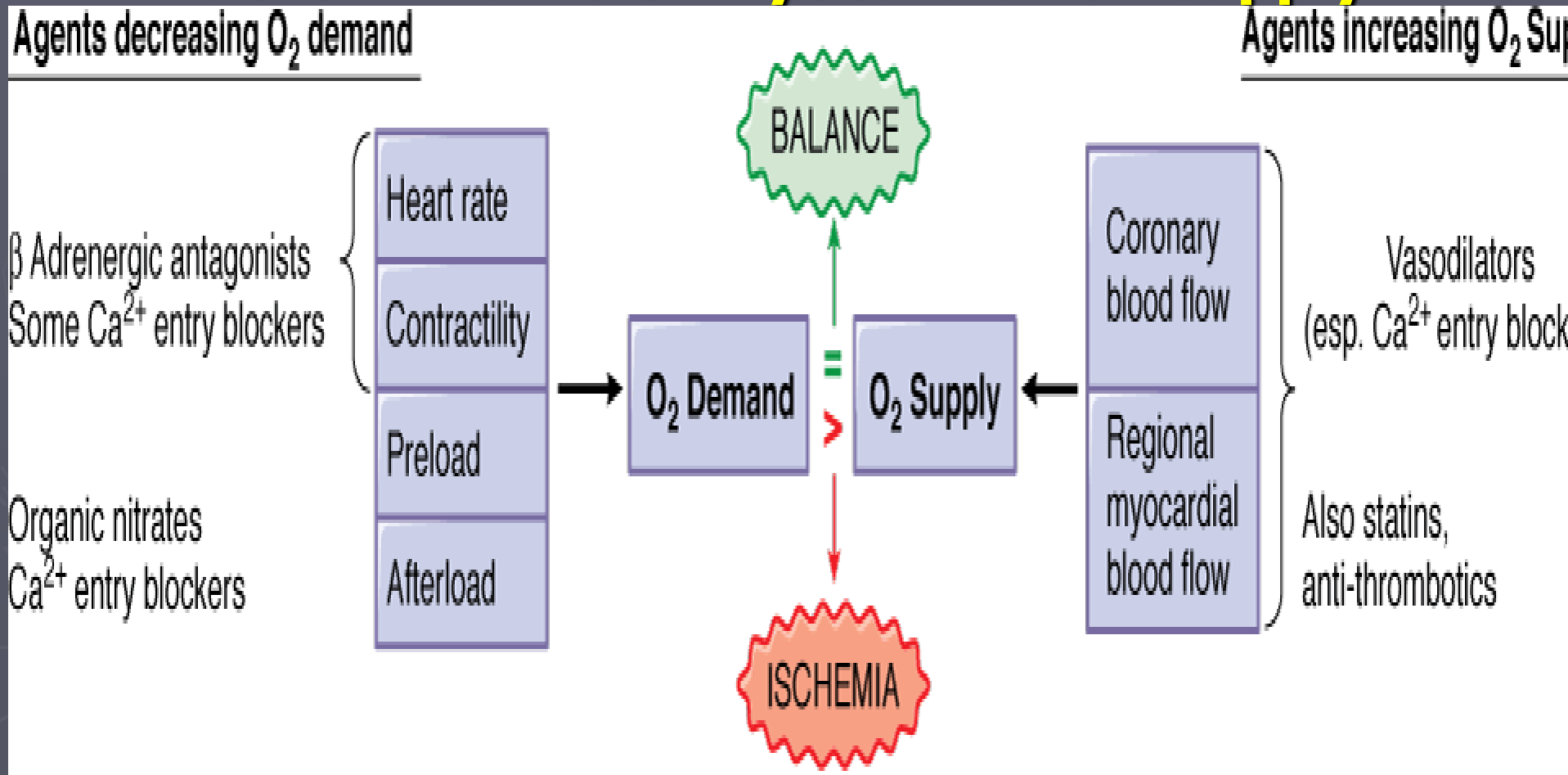
O_2 Supply (Coronary Blood Flow)

O_2 Demand (Work of the Heart)

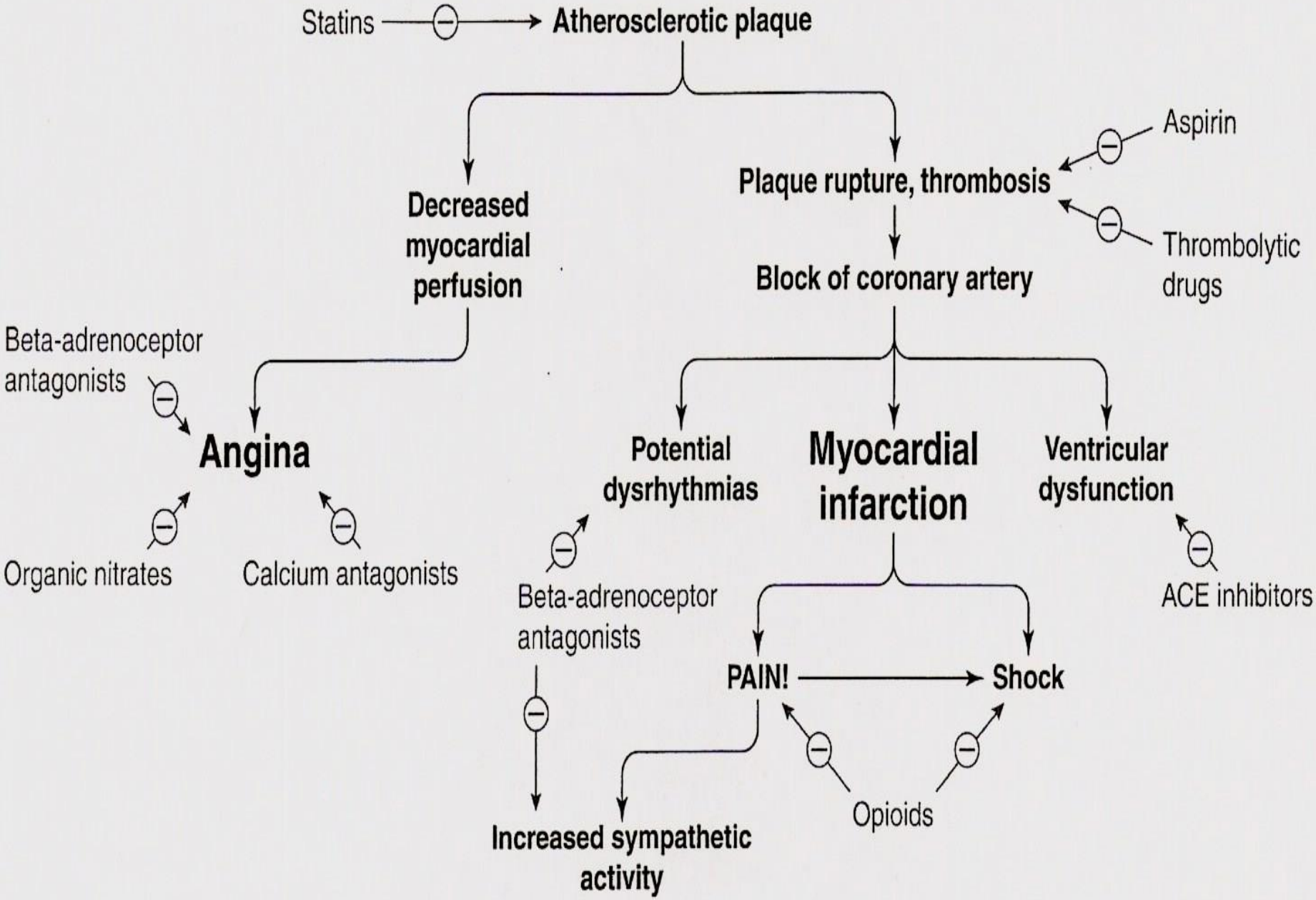
Major Determinants of Myocardial Oxygen Supply and Demand

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 O2 supply



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com



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

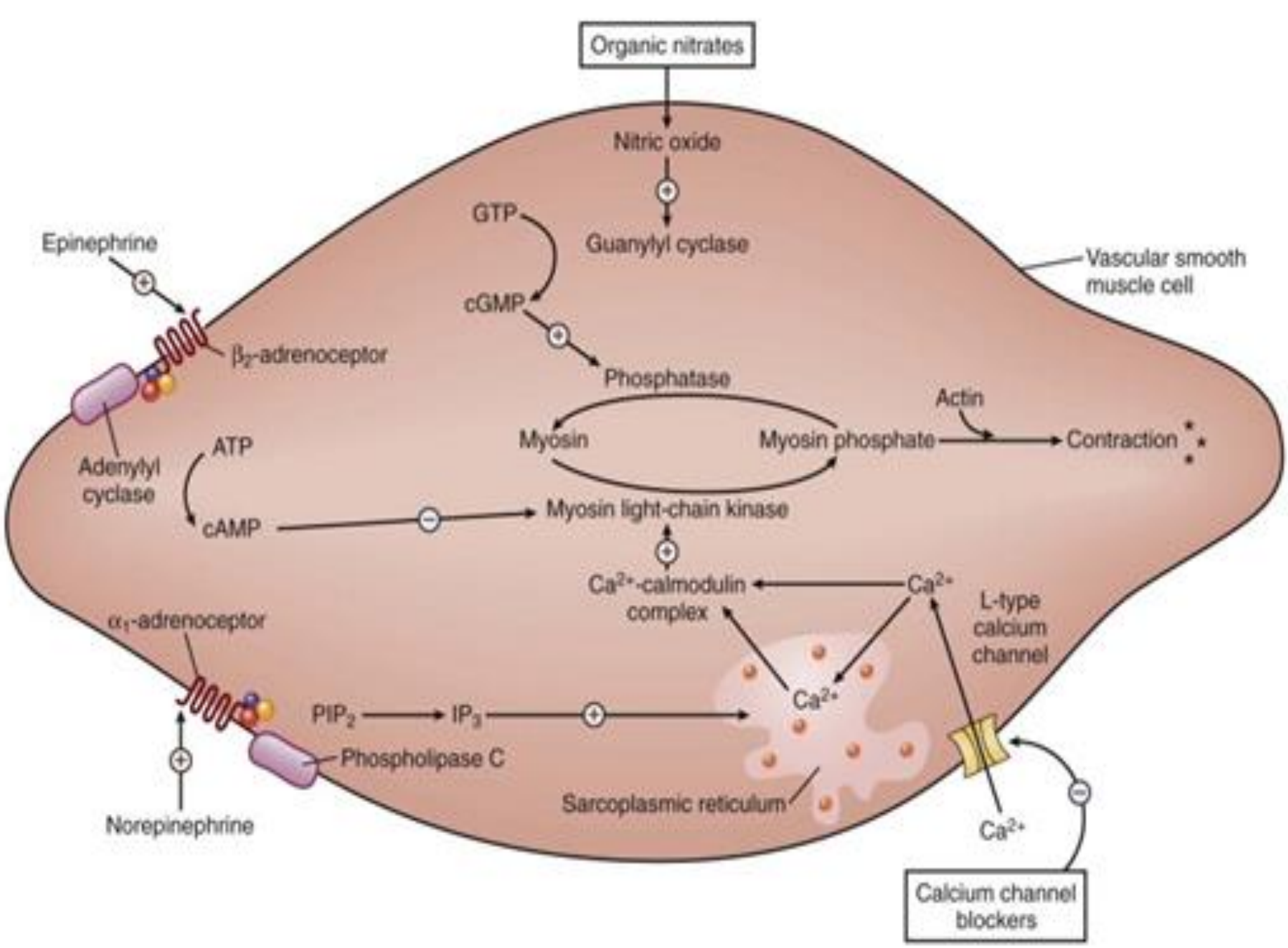
Drug effects on vascular smooth muscle contraction.

- Calcium influx is inhibited by CCBs, leading to muscle relaxation.

- Organic nitrates release nitric oxide, which activates guanylyl cyclase and increases formation of cyclic guanosine monophosphate.
  - cGMP causes smooth muscle relaxation by activating kinases that increase myosin phosphatase activity and decrease myosin phosphate levels.

- α 1-Adrenoceptor agonists activate phospholipase C (PLC), which increases formation of inositol triphosphate (IP 3) from phosphatidylinositol bisphosphate (PIP 2), leading to increased release of calcium from the sarcoplasmic reticulum.

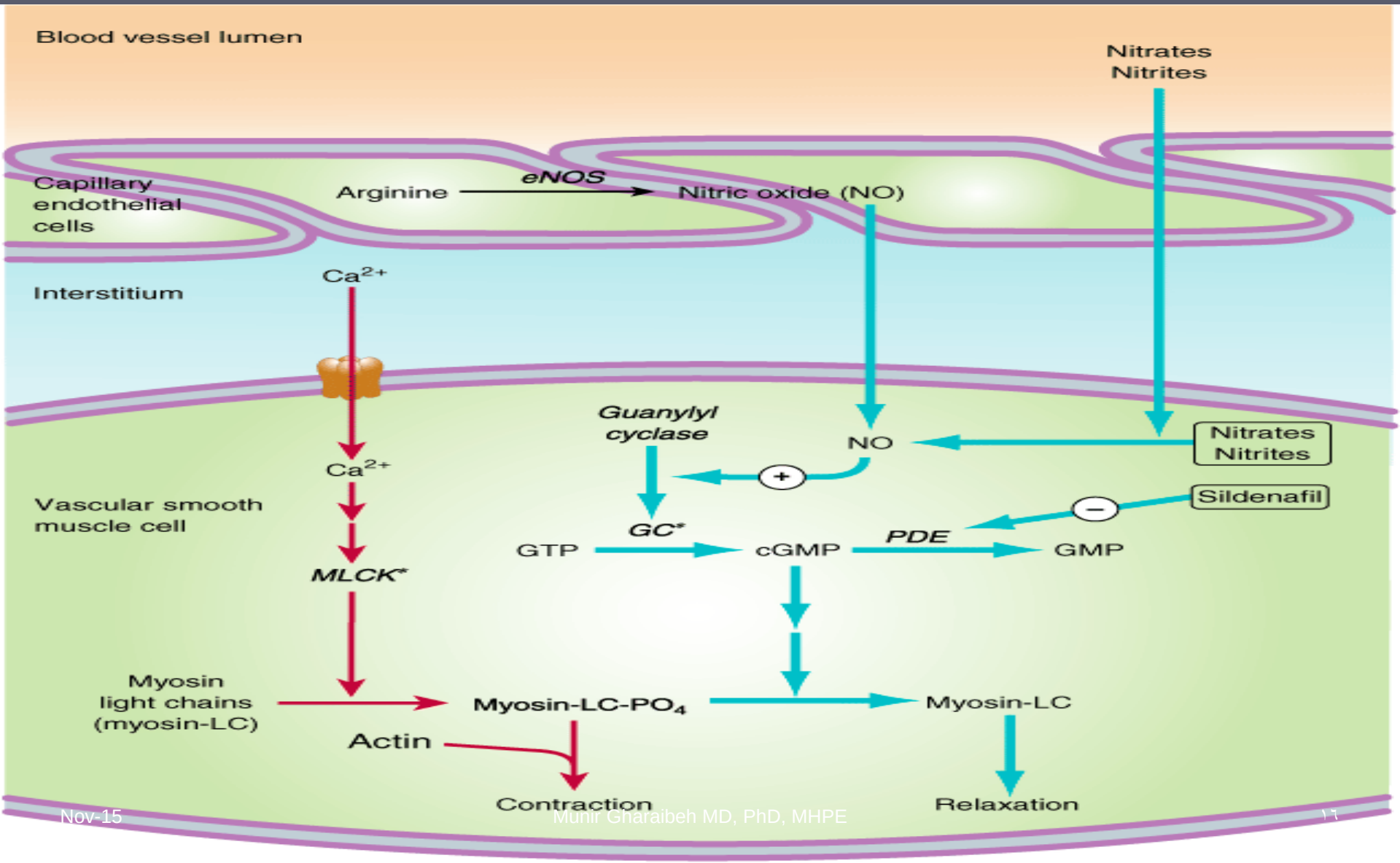
- β 2-Adrenoceptor agonists increase formation of cyclic adenosine monophosphate (cAMP), which activates kinases that inhibit myosin light-chain kinase.


Organic nitrates
Nitric oxide
GTP
Guanylyl cyclase
Epinephrine
Vascular smooth muscle cell
cGMP
β2-adrenoceptor
Phosphatase
Actin
Myosin
Myosin phosphate
Contraction
ATP
Adenylyl cyclase
cAMP
Myosin light-chain kinase
Ca2+-calmodulin complex
Ca2+
L-type calcium channel
α1-adrenoceptor
PIP2
IP3
Ca2+
Phospholipase C
Sarcoplasmic reticulum
Norepinephrine
Ca2+
Calcium channel blockers

Organic Nitrates

- **Nitroglycerine (GTN):**
- Prototype, used for more than 140 years.
- Nonspecific smooth muscle relaxant.
- Action not antagonized by any known antagonist.

Nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in vascular muscle



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*,

Nitroglycerine (GTN)

- Usually administered sublingually.
- Can be administered by various routes.
- Fast onset of action(1-3minutes, Peaks at 10 minutes).
- Short duration (15-30minutes).
- Reductase enzyme in liver will breakdown the drug.

Nitroglycerine (GTN)

- ***Causes general vasodilation:***
- **Arteriolar dilation: short lived (5-10 min)**
  - **Decreases systemic blood pressure (afterload) and causes reflex tachycardia and increased contractility, ?might increase MVO2.**
- **Venous dilation: more intense, even with low doses, lasts for 30 minutes.**
  - **Decreases venous return (preload) and decreases MVO2.**

Figure 19-2
A schematic drawing indicating the major actions of the nitrates on the ischemic heart and peripheral circulation. ↓ = decrease; ↑ = increase; → = unchanged; ⇵ = variable effect.

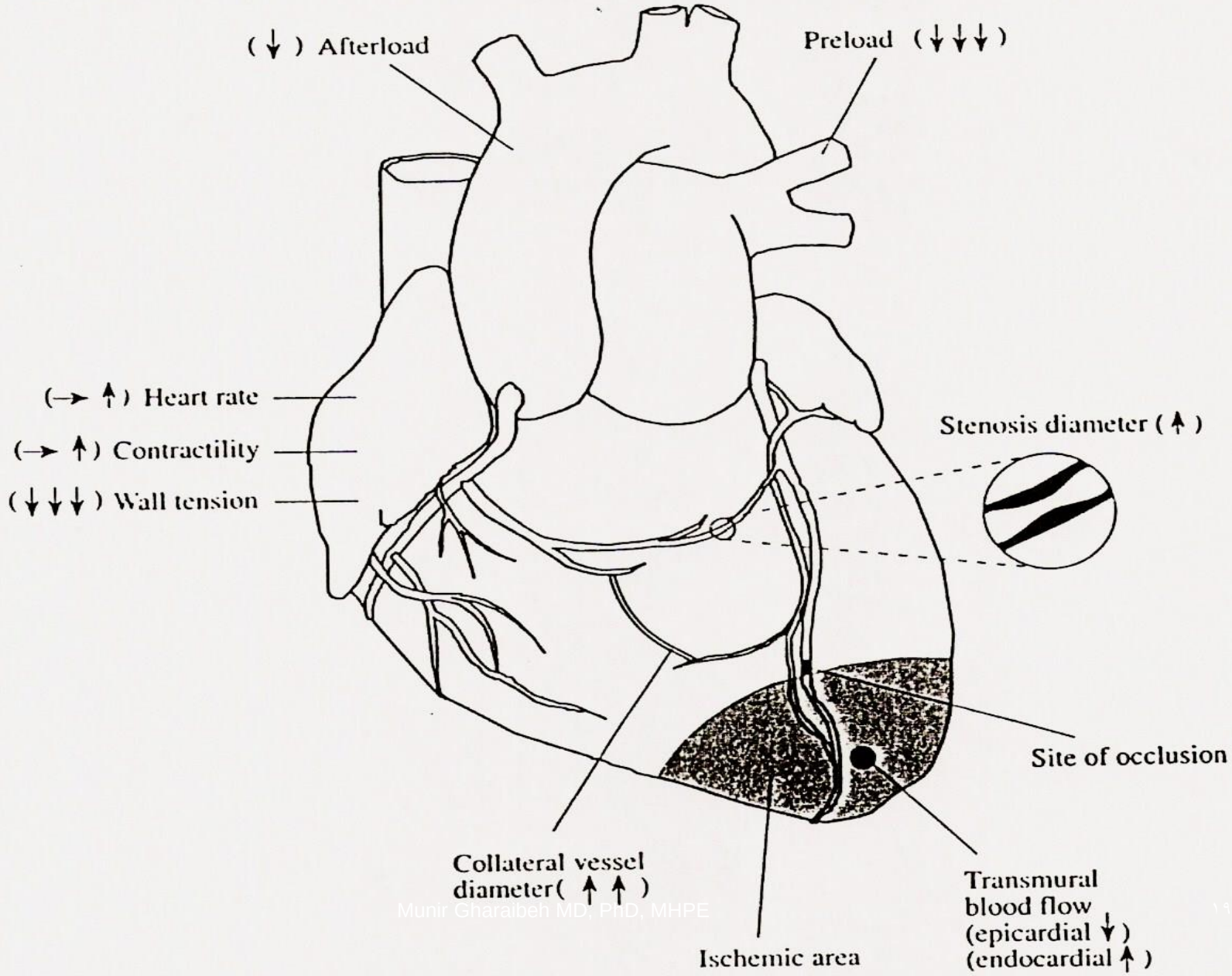


Table 12–2 Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina.

Effect	Result
Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement
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
Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	Increased myocardial oxygen requirement
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

Nitroglycerine (GTN)

- **Side Effects:**
- Headache.
- Hypotension and tachycardia.
- Increased intraocular and intracranial pressures.
- Methemoglobinemia.
- Tolerance: only for the arteriolar effects.
- Withdrawal: in workers in ammunition industry.

Preparations of Nitrate

Drug	Duration of Action
Short-acting:	
Nitroglycerin, sublingual	10–30 minutes
Isosorbide dinitrate, sublingual	10–60 minutes
Amyl nitrite, inhalant	3–5 minutes
Long-acting:	
Nitroglycerin, oral sustained-action	6–8 hours
Nitroglycerin, 2% ointment, transdermal	3–6 hours
Nitroglycerin, slow-release, buccal	3–6 hours
Nitroglycerin, slow-release patch, transdermal	8–10 hours
Isosorbide dinitrate, sublingual	1.5–2 hours
Isosorbide dinitrate, oral	4–6 hours
Isosorbide dinitrate, chewable oral	2–3 hours

Beta Adrenergic Blockers

- Prevent actions of catecholamines, so more effective during exertion.
- Do not dilate coronary arteries, might constrict them.
- Do not increase collateral blood flow.
- Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.

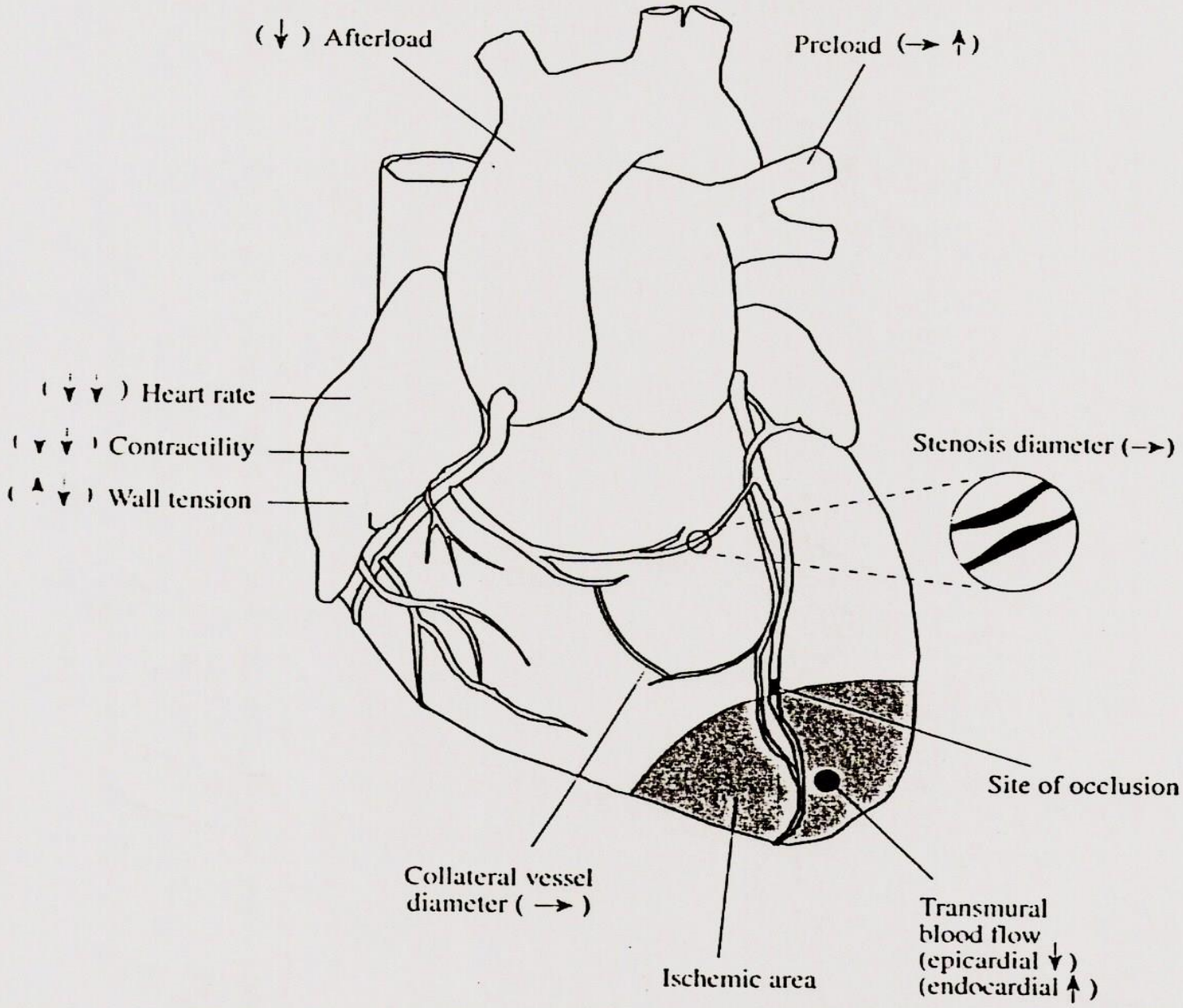


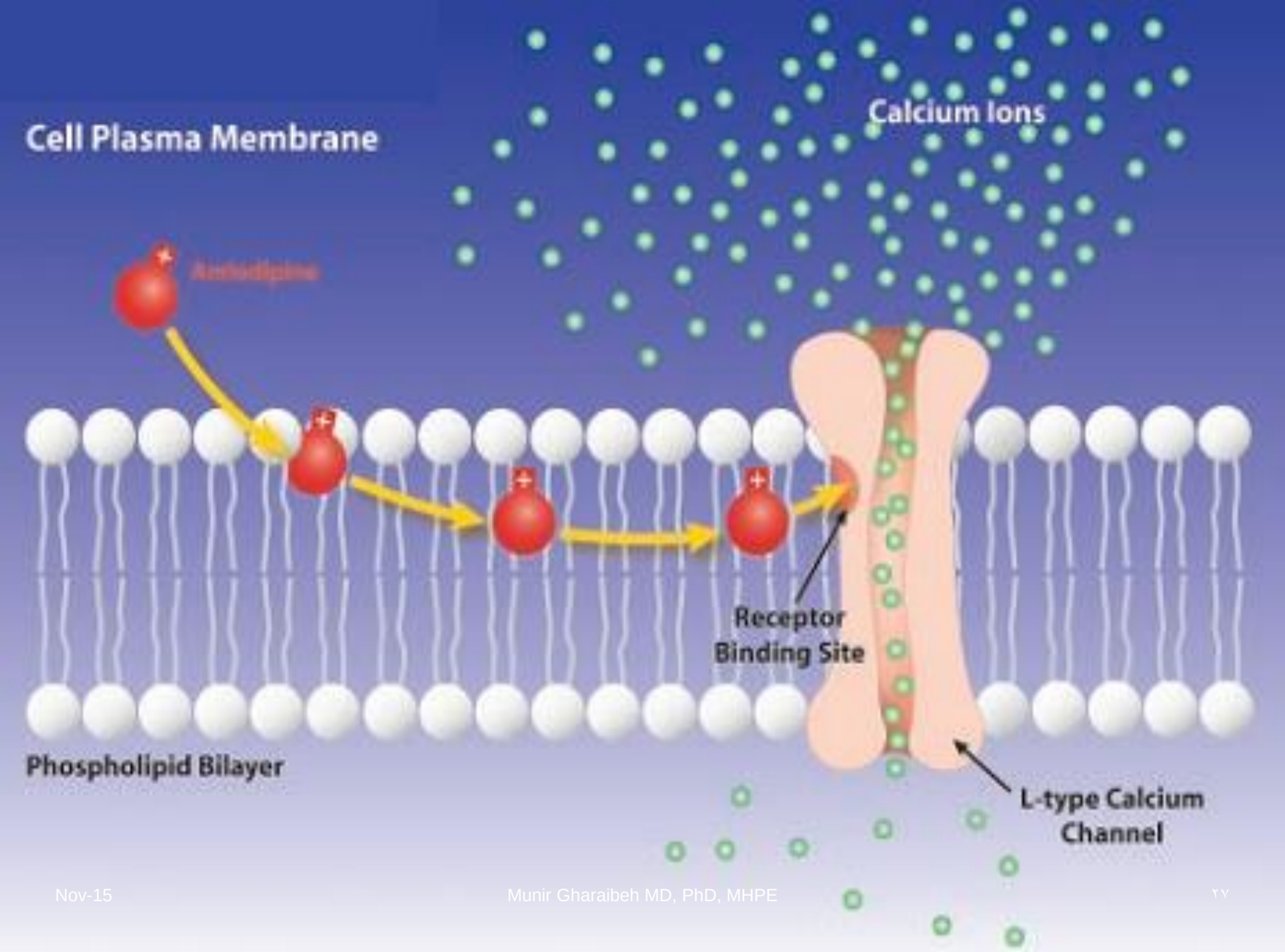
Figure 19-3
A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. For key, see Fig. 19-2.

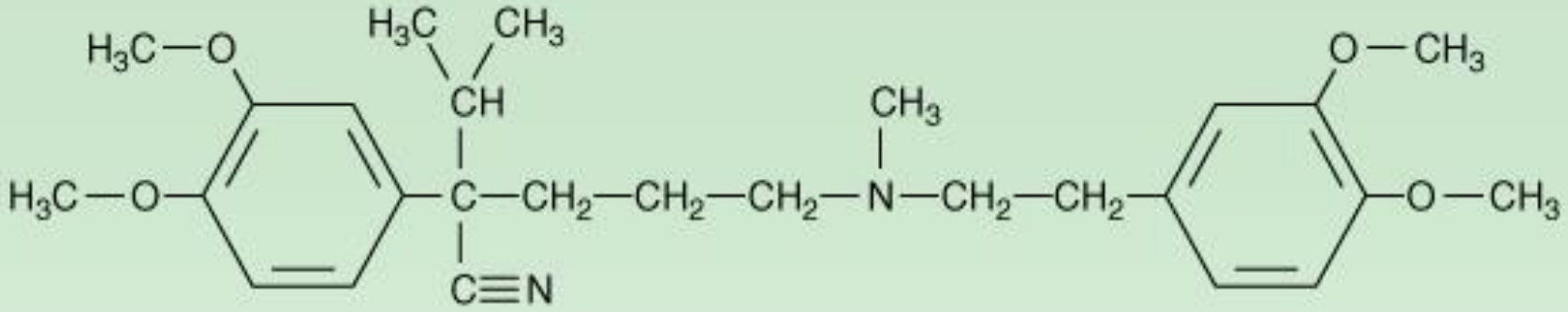
Calcium Channel Blockers

- Particularly beneficial in vasospasm.
- Can affect platelets aggregation.
- May be dangerous in the presence of heart failure and in patients susceptible to hypotension.

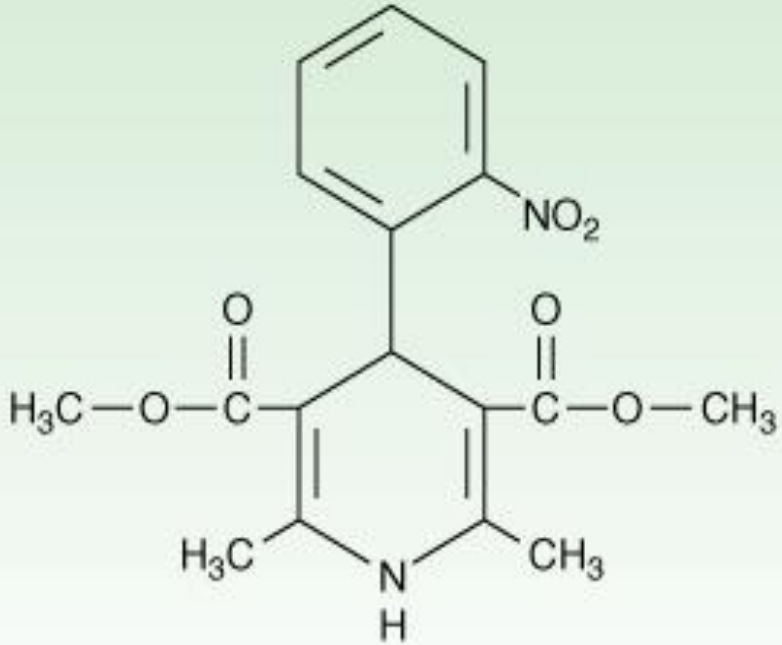
Properties of Several Recognized Voltage-Activated Calcium Channels.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, -aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] -CTX-GVIA, -aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	-CTX-MVIIC, -aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, -aga-IIIA

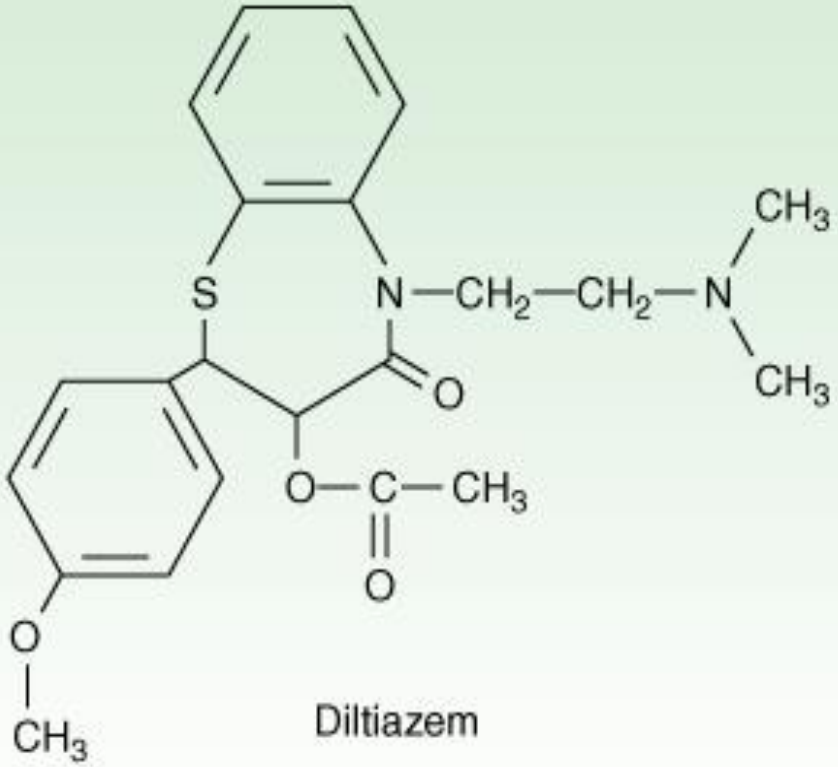

Cell Plasma Membrane
Calcium Ions
Receptor
Binding Site
Phospholipid Bilayer
L-type Calcium
Channel



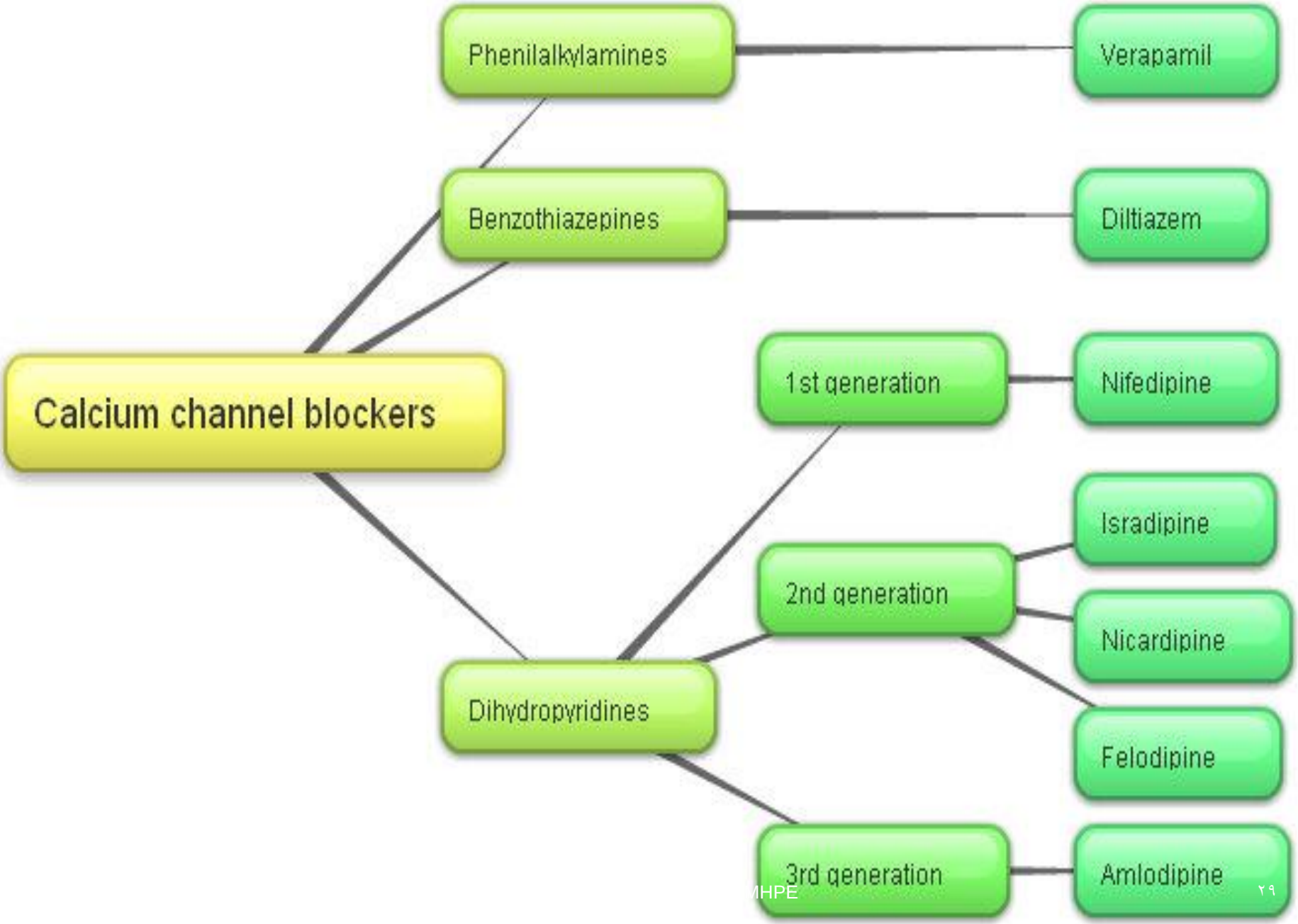
Verapamil



Nifedipine



Diltiazem


Calcium channel blockers
Phenilalkylamines
Verapamil
Benzothiazepines
Diltiazem
Dihydropyridines
1st generation
Nifedipine
2nd generation
Isradipine
Nicardipine
Felodipine
3rd generation
Amlodipine

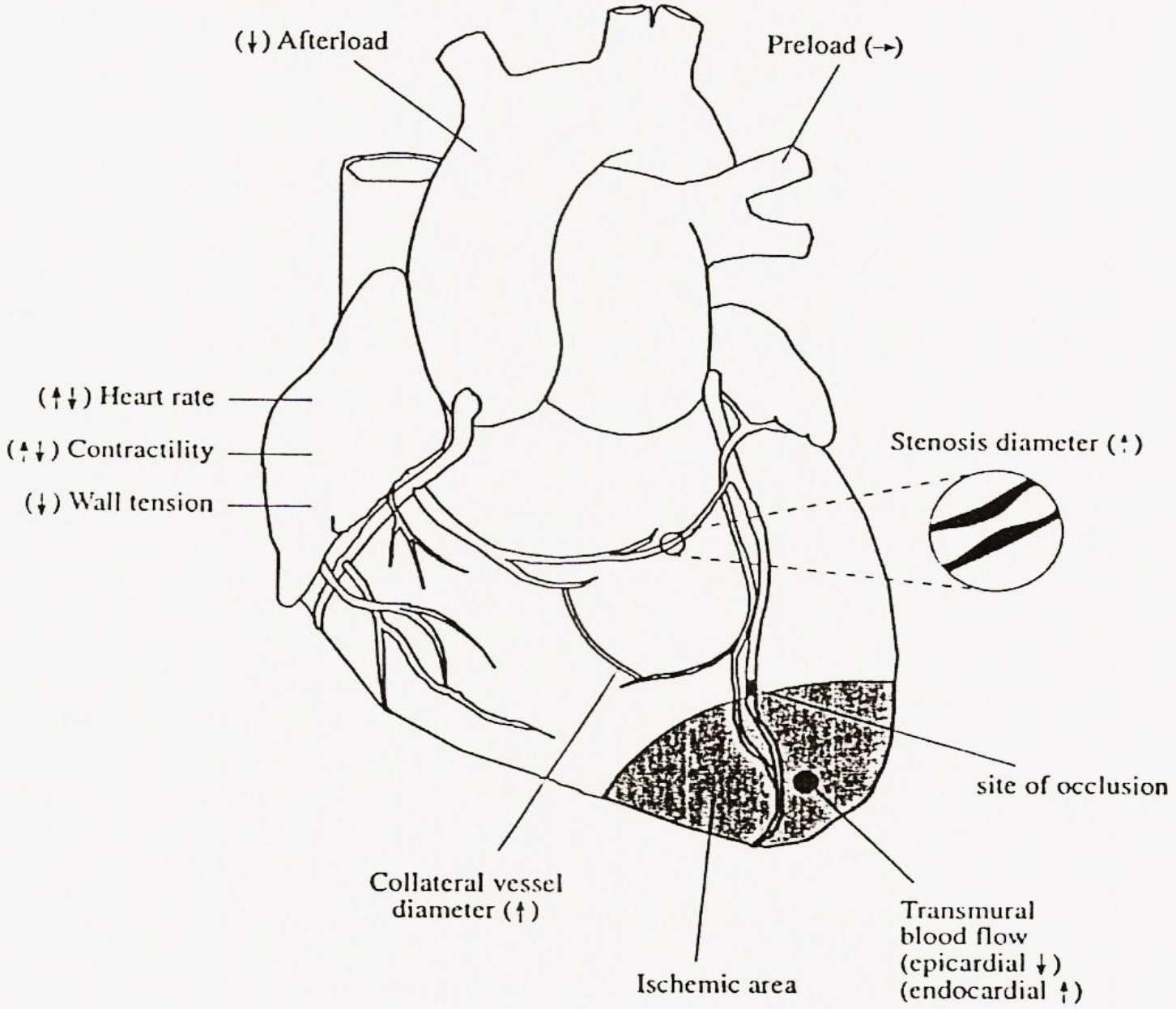


Figure 19-4

A schematic drawing indicating the major actions of the calcium antagonists on the ischemic heart and coronary circulation. For key, see Fig. 19-2.

Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
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
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

Calcium Channel Blockers

- **Side Effects:**
- Hypotension.
- Headache, dizziness.
- Flushing.
- Peripheral edema.

Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.

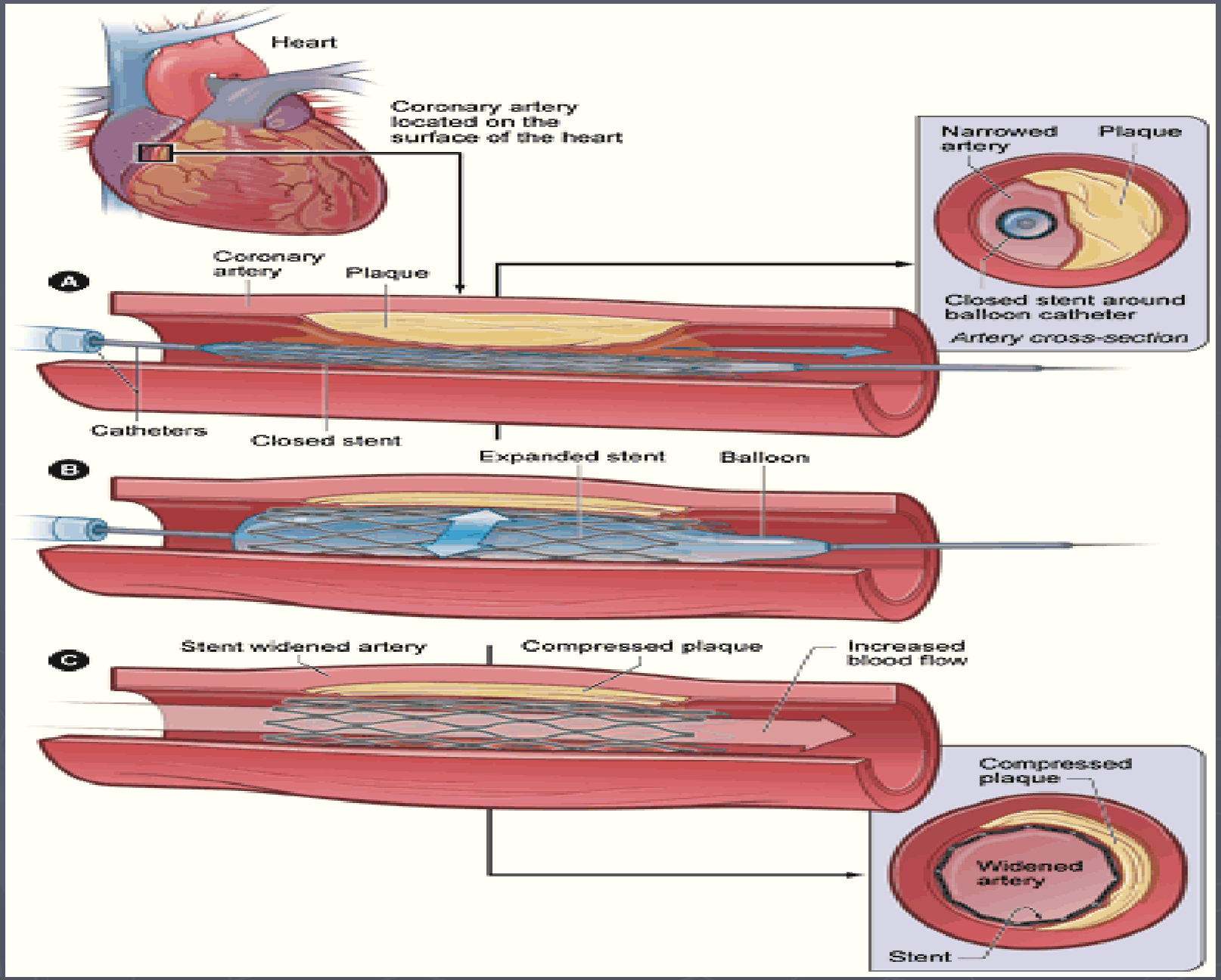
	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	*Reflex[1] increase*	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	Increase	Non or decrease
Contractility	*Reflex[1] increase*	Decrease	Non
Ejection time	Decrease	Increase	Non

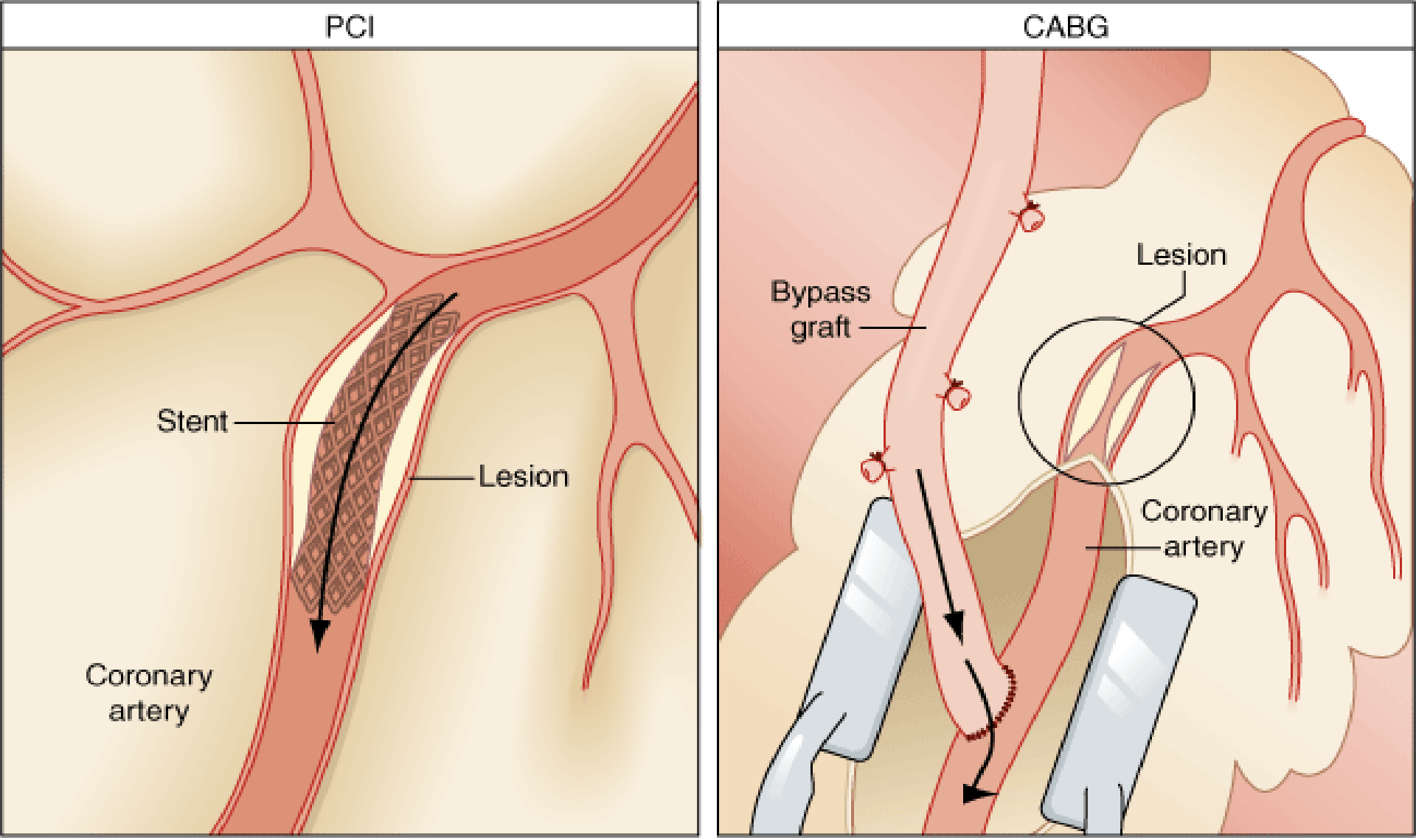
Dipyridamole

- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.
- Thought to be a good coronary dilator.
- Increases the blood flow to the normal area i.e. **"Coronary Steal Phenomenon".**
- Still used as an antiplatelet drug (in TIAs), but not better than aspirin.

Others

- ACEI.
- Anticoagulants and/or Thrombolytic Therapy.
- Cholesterol Lowering Agents.
- Angioplasty
- Surgery.


Heart
Coronary artery located on the surface of the heart
Narrowed artery
Plaque
Closed stent around balloon catheter
Artery cross-section
A
Coronary artery
Plaque
Catheters
Closed stent
B
Expanded stent
Balloon
C
Stent widened artery
Compressed plaque
Increased blood flow
Compressed plaque
Widened artery
Stent



Stent addresses the existing lesion but not future lesions.

Bypass grafting addresses the existing lesion and also future culprit lesions.

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Newer Antianginal Drugs

- Metabolic modulators: Ranolazine.
- Direct bradycardic agents: Ivabradine.
- Potassium channel activators: Nicorandil.
- Rho-kinase inhibitors: Fasudil.
- Sulfonylureas: Glibenclamide.
- Thiazolidinediones.
- Vasopeptidase inhibitors.
- Nitric oxide donors: L- arginine.
- Capsaicin.
- Amiloride.