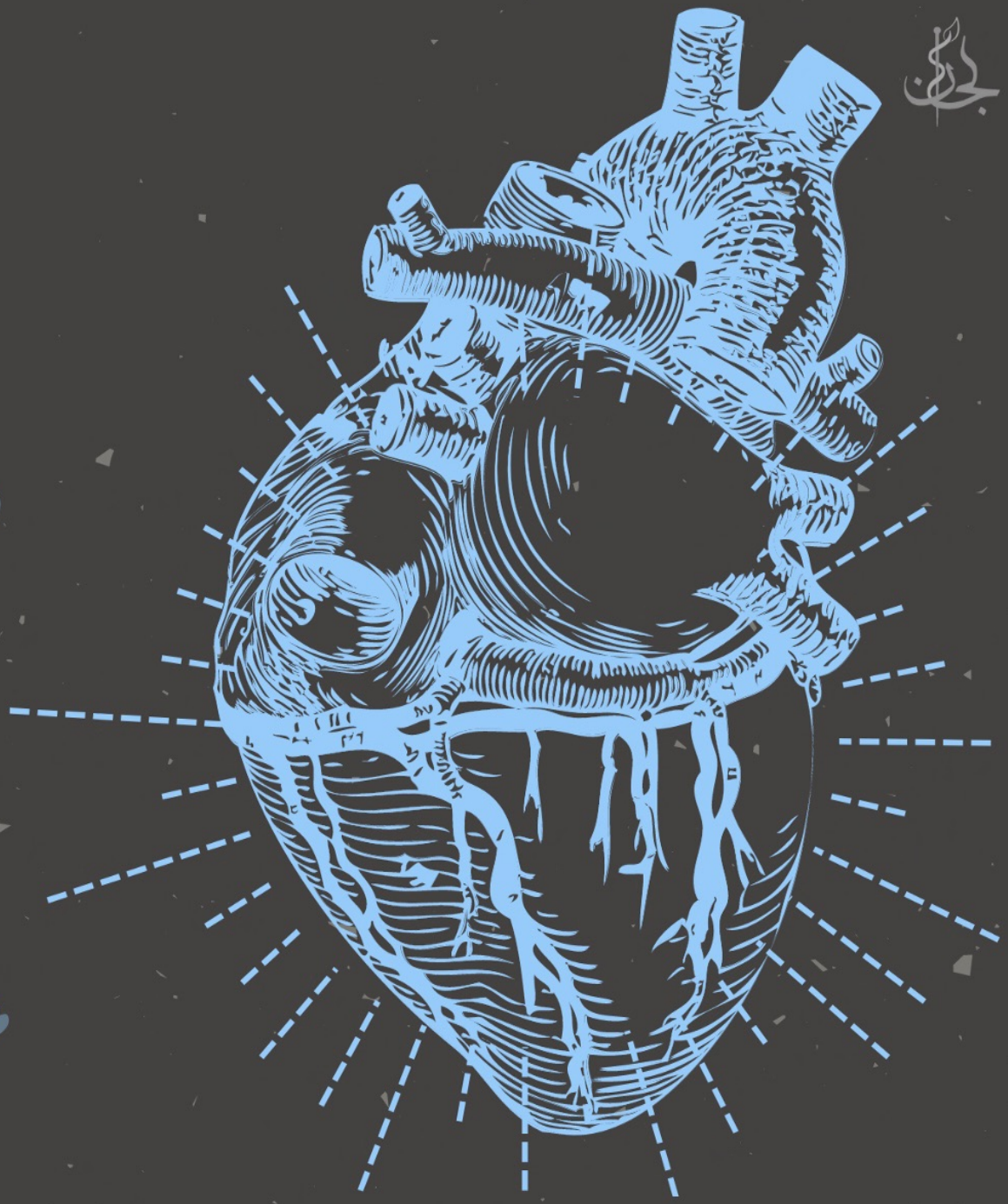
CVS



PHARMACOLOGY

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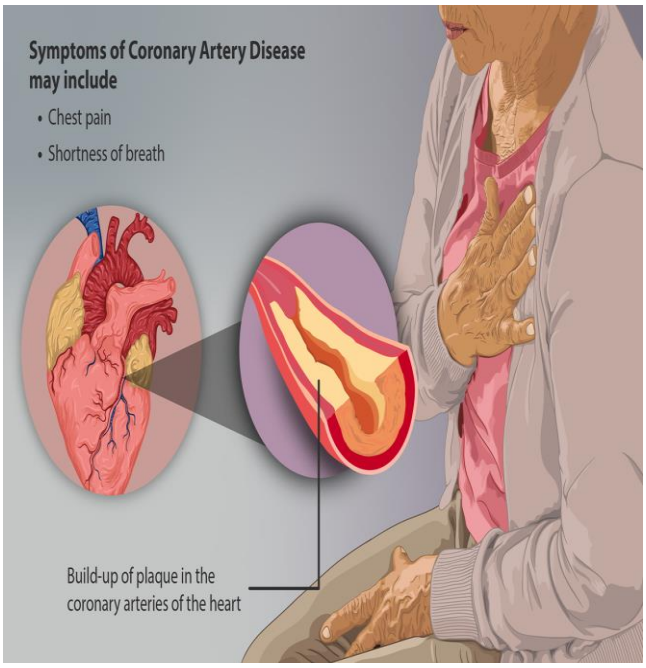
What Is An Ischemic Heart Disease? *You can skip this page (Extra)*

Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or coronary heart disease, is the most common cause of mortality worldwide. Atherosclerotic lesions in coronary arteries can obstruct blood flow, leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome (myocardial infarction [MI] or unstable angina). Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and anginal pain.



Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms. Patients may also present with dyspnoea or atypical symptoms such as indigestion, nausea, vomiting, or diaphoresis. Transient, self-limited episodes of myocardial ischemia (stable angina) do not result in cellular death; however, acute coronary syndromes and chronic ischemia can lead to deterioration of cardiac function, heart failure, arrhythmias, and sudden death.

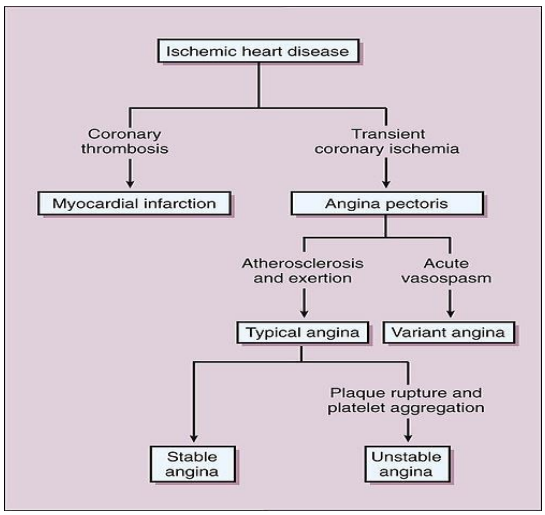
All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation, physical activity, weight management) and management of modifiable risk factors (hypertension, diabetes, dyslipidaemia) to reduce cardiovascular morbidity and mortality.

CASE STUDY (extra)

A 56-year-old woman presents in the office with a history of recent-onset chest discomfort when jogging or swimming vigorously. The pain is dull but poorly localized; it disappears after 5–10 minutes of rest. She has never smoked but has a history of hyperlipidaemia (total cholesterol level of 245 mg/dL and low-density lipoprotein [LDL] of 160 mg/Dl recorded 1 year ago) and admits that she has not been following the recommended diet. Her father survived a “heart attack” at age 55, and an uncle died of some cardiac disease at age 60. On physical examination, the patient’s blood pressure is 145/90 mm Hg, and her heart rate is 80 bpm. She is in no acute distress, and there are no other significant physical findings; an electrocardiogram is normal except for slight left ventricular hypertrophy. Assuming that a diagnosis of stable effort angina is correct, **what medical treatment should be implemented**?

"Ischemic heart disease types include angina pectoris and **Myocardial Infarction** (tissue death), which may lead to **heart failure** and **cardiac arrhythmias**".

Types of Angina *(chest pain)*



- Angina pectoris has three patterns:

  1) Stable, effort-induced, classic, or typical angina.

  2) Unstable angina.

  3) Prinzmetal, variant, vasospastic, or rest angina.

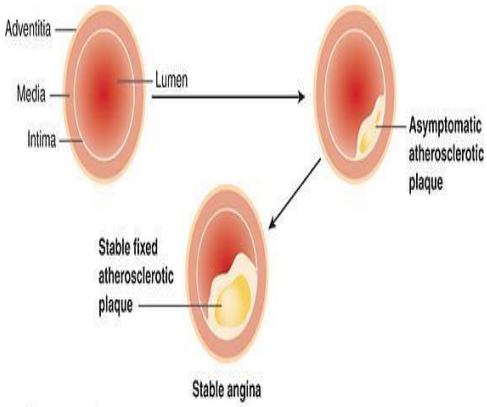
- They are caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

- Stable angina, if untreated, may become unstable angina, which may progress to myocardial infarction.

- The word **secondary** in "secondary angina" indicates that this type of angina is secondary to atherosclerosis.
- The word **primary** in "primary angina" indicates that there is no primary cause, but it is due to a functional abnormality, which is vasoconstriction in the major coronary arteries.
  Primary angina was described by Prinzmetal.

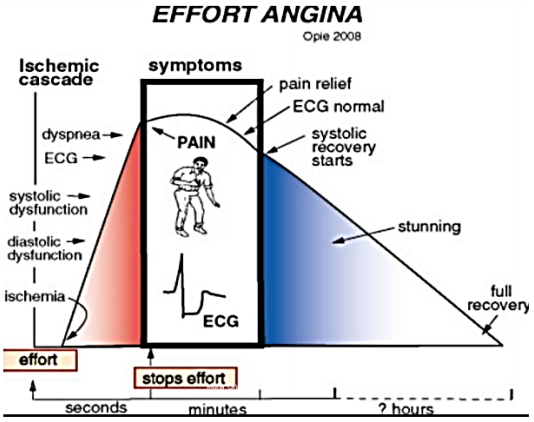
- Secondary Angina may occur in a single or multiple small vessels. This is because atherosclerosis (systemic disease) may take place in more than one small vessel (all over the heart).
- Primary angina usually involves a single coronary artery=> which causes the symptoms.

- Secondary Angina => **ST depression**
- Primary Angina => **ST elevation**



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

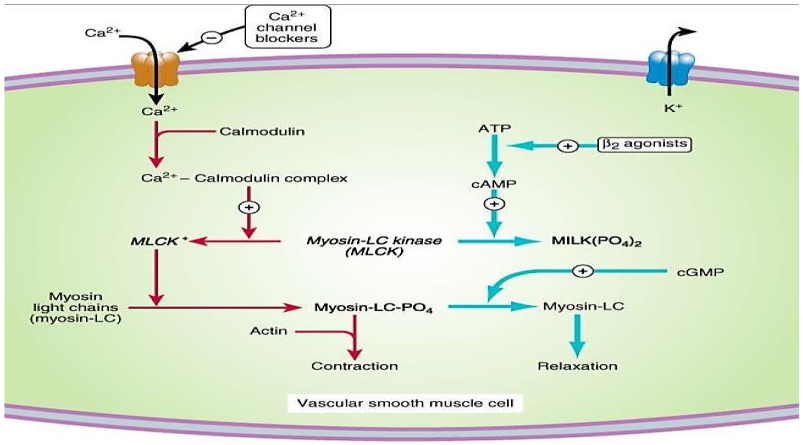
1. Stable angina, effort-induced angina, classic or typical angina



- Precipitated by effort, of short duration, and easily relieved (just stop your exercise/effort/stress).
- Classic angina is caused by the reduction of coronary perfusion due to **a fixed obstruction of a coronary** artery produced by atherosclerosis.
  Due to the fixed obstruction, the blood supply cannot increase, and the heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity (stair climbing), emotional (psychological) stress or excitement, or any other cause of increased cardiac workload.
- Effort=>ischemia=>diastolic and systolic dysfunctions, which are associated with <u>excruciating chest pain, dyspnea and a change in **ECG (ST Depression).**</u>
  The patient reaches the hospital after the pain is relieved, ECG will be **normal.**
- Pain typically starts from chest and radiates into the arm, shoulder, leg and upper & lower left jaws. Patients may just complain from the radiated pain. Diabetic patients (neuropathy) may not complain from pain but dyspnea, instead.
- **Myocardial stunning** is the <u>reversible</u> (meaning that it completely resolves) <u>reduction</u> of function of heart contraction after **reperfusion** (this is what causes the phenomenon) which is not due to the damaged tissue or reduced blood flow.

Control of smooth muscle contraction

- Contraction is triggered by:
  1) Influx of **extracellular** calcium through L-type transmembrane calcium channels.
  2) Calcium combines with calmodulin to form a complex that converts the enzyme **myosin light-chain kinase** to its active form (MLCK*).
  3) 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 **<u>smooth</u>** muscle by **accelerating** the inactivation of MLCK leading to its phosphorylation (look at the figure below) and by facilitating the expulsion of calcium from the cell.

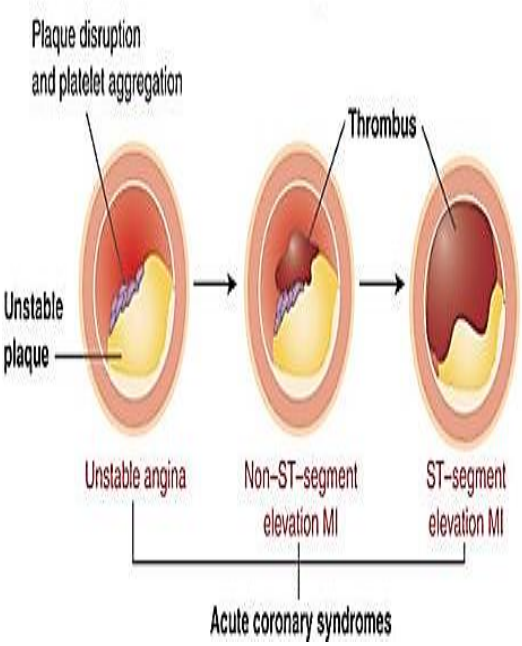


← cGMP can also cause smooth muscle relaxation through dephosphorylating "Myosin light chain phosphate".

Extra info (the whole page)

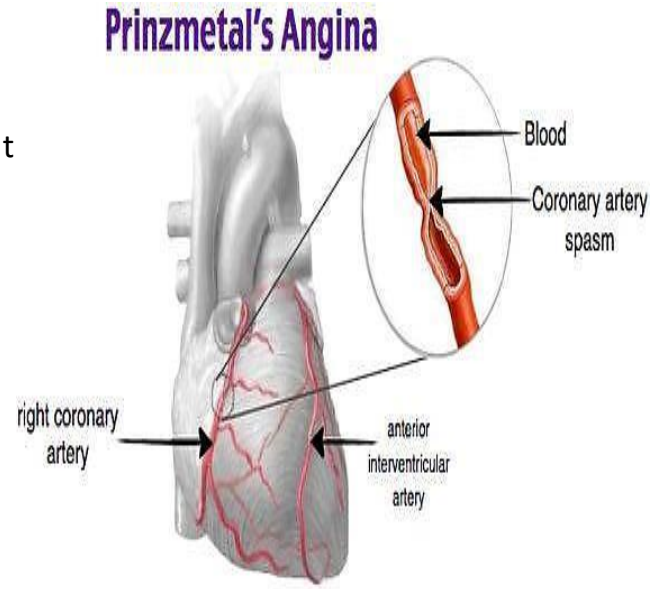
2. Unstable Angina

- **Unstable angina,** an **acute coronary syndrome,** is said to be present when episodes of angina occur at rest and there is an increase in the severity, frequency, and duration of chest pain in patients with previously stable angina. Unstable angina is caused by episodes of increased epicardial coronary artery resistance or small platelet clots occurring in the vicinity of an atherosclerotic plaque. In most cases, formation of labile partially occlusive thrombi at the site of a fissured or ulcerated plaque is the mechanism for reduction in flow.
- Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death
- Nitroglycerin tablets are **not** helpful.



3. Prinzmetal, variant, vasospastic, or rest angina

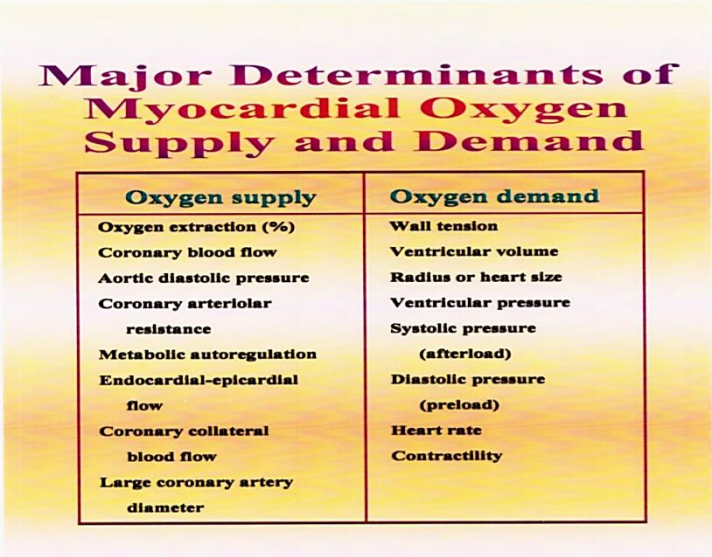
- Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure.
- Nitroglycerin tablets are helpful.
- ECG: ST elevation



Pathophysiology of Angina

We already understand the fact that ischemic heart disease (IHD) takes place when there is an imbalance between the O2 **demand/consumption** (work of the heart) and **supply** (coronary blood flow).

So, what are the determinants of myocardial oxygen *Demand* and *Supply*?



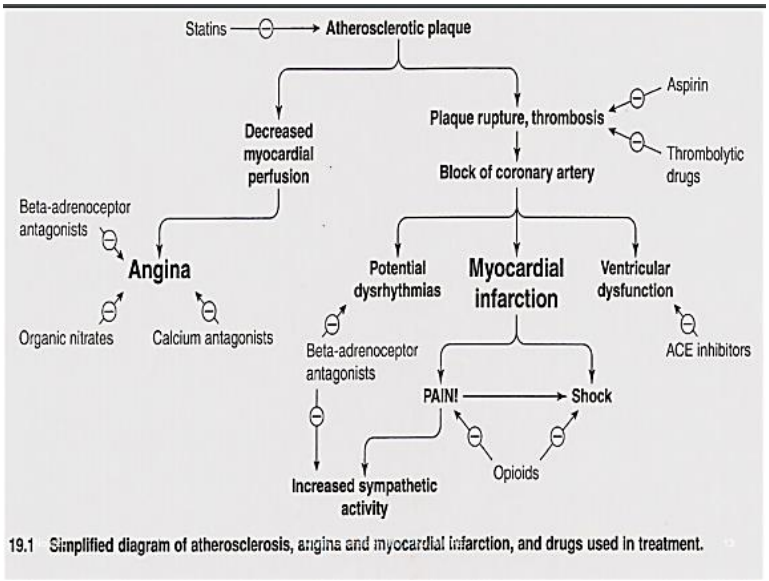
Notes related to the table

- As blood passes through the arterial side of the capillary, the tissue it supplies tries to grab or extract as much O2 as it can.
  Tissues differ in their O2-extracting capabilities; some tissues are slow O2-capturers, and are only able to capture a small fraction of the O2 in blood => they have low O2-extracting capabilities. Other tissues, however, have **high O2-extracting capacities** (like the heart). But, oxygen extraction has a limit (for instance, the maximum oxygen that can be extracted from blood is 20% for any tissue).
  Tissues that have **low** oxygen extraction percentages (e.g. 1-5%) can increase their oxygen extraction ability if they need to (they can increase it up to 20%... or close to it at least). Tissues with **high** O2 extracting capacities (like the heart ... around 10-15%) are already working at optimal oxygen extracting capacity, and so if they are challenged with increased demand, they can't increase their oxygen extraction by a lot (remember the limit .. 20%) and so they need to look for other ways to increase their oxygen supply.
  You really do not have to memorize any of the above-mentioned. Just understand the concept.

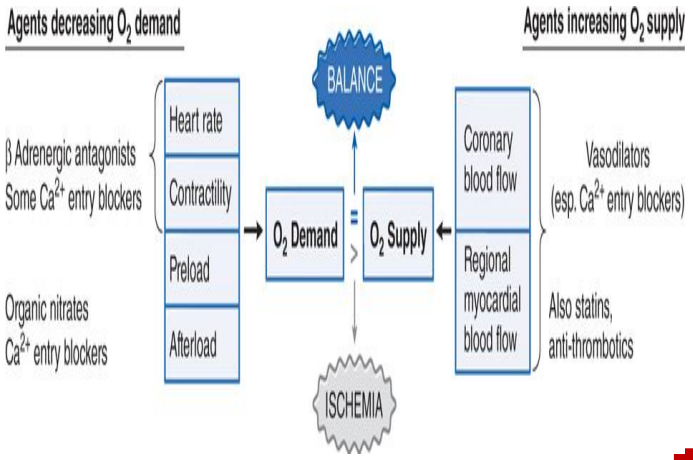
  So to sum up: If a tissue has increased O2 demand, it can increase its oxygen extraction rate. This is true for almost all tissues but the heart, which is already working at near maximal O2 extraction rate.
- Coronary blood flow mainly occurs during **diastole**.
- In cases of severe **hypotension**, **dehydration**, or **bleeding**, there will be a decrease in the coronary blood flow.
- As the coronary arteriolar resistance increases due to vasoconstriction, for example, coronary blood flow will decrease.

- The **main** factor in determining oxygen supply is the **metabolic autoregulation.** Myocardial cells may depend on the presence of certain metabolites, like **adenosine**, in causing vasodilation and ultimately increasing blood flow through the coronary arteries. This is true in certain conditions, for example, under stress/ischemia; myocardial cells are maximally auto-regulated as there will be maximal dilatation (caused by the generation of adenosine) in the blood vessels **near the area of ischemia**. That is why we cannot further increase the diameter (blood flow) of these small blood vessels during ischemia.
- As the intraventricular pressure increases, the flow of blood to endocardial cells is reduced, while the blood flow to epicardial cells increases. This might cause some sort of ischemia.
- The concept of coronary collateral circulation/blood flow is very important, because when one area of the heart becomes ischemic, collateral circulation will develop between the non-ischemic and ischemic regions, and due to the pressure gradient (difference in pressure between the two regions), blood flows from the normal area to the ischemic area.

You must be familiar with the figures below *(the professor read every word in them)*



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



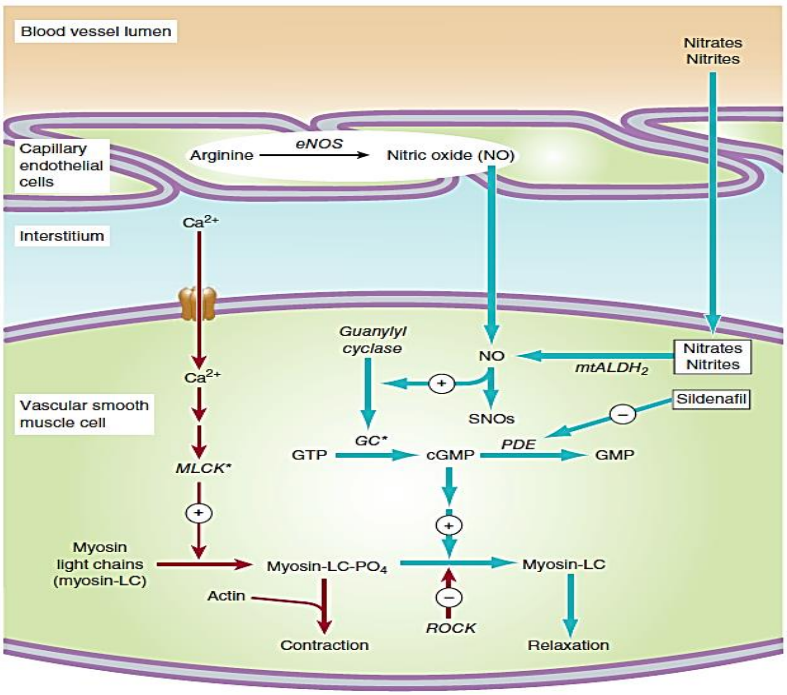
Organic Nitrates

- Nitroglycerin, also known as glyceryl trinitrate (GTN), may be considered the prototype of the group and has been used in cardiovascular conditions for over (150-160 yrs.)
- These drugs are considered to be non-specific (general) **smooth muscle** relaxant.
- These drugs show more selectivity toward the venous side of circulation.

Mechanism of Action in Smooth Muscle

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to **dephosphorylation** of the myosin light chain, resulting in vascular smooth muscle relaxation.

Nitrates such as Nitroglycerin **mainly** cause (1) dilation of the large veins (and (2) to less extent arteries, reducing the TPR by dilating them), which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart. This is believed to be their main mechanism of action in the treatment of angina. Nitrates also (3) dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

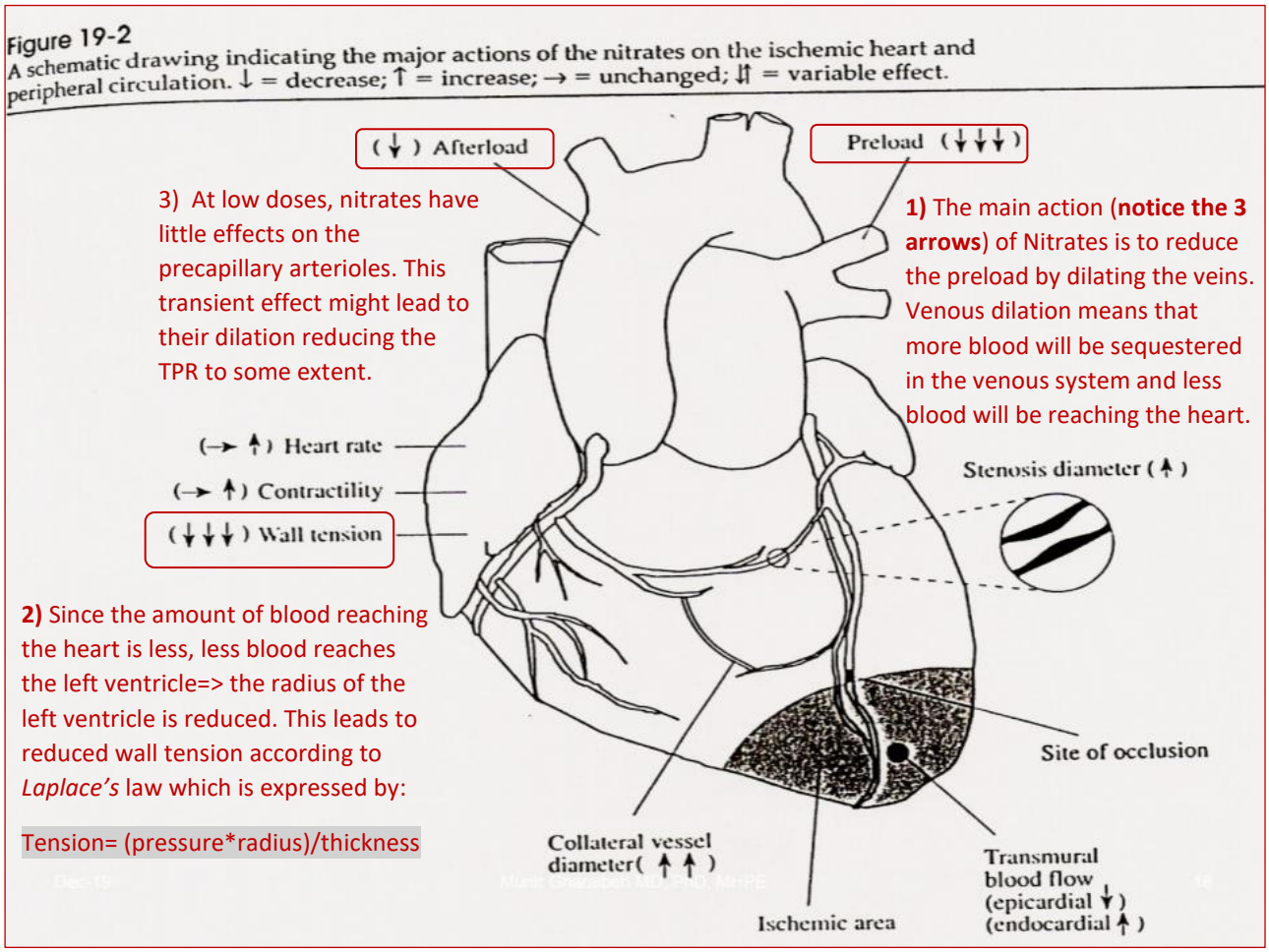


Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (cells. Steps leading to relaxation are shown with blue arrows. MLCK*, activated myosin light-chain kinase (see F Os) appear to have non-cGMP-dependent effects on potassium channels and Ca^{2+}-ATPase. eNOS, endothelial ivated guanylyl cyclase; $mtALDH_2$, mitochondrial aldehyde dehydrogenase-2; PDE, phosphodiesterase; ROCK, Rl

Sildenafil (Viagra) inhibits PDE CGMP (phosphodiesterase CGMP) → vasodilation → ↑ blood flow → erectile response.

Extra: If used concomitantly with nitrates or other potent vasodilators, the excessive fall in blood pressure may lead to death from cardiovascular causes, including myocardial infarct.

Nitrates Action On the cardiovascular system



We aim to reduce the oxygen consumed by the heart, so far we are doing great. Oops, not really!! ☹

Actually, we were successful in reducing the preload & the wall's tension significantly, and so the O2 required to supply the heart was less. But, the indirect effects of Nitroglycerin which consist of those compensatory responses evoked by baroreceptors and hormonal mechanisms responding to decreased arterial pressure result in **tachycardia** and increased **cardiac contractility** (clearly seen when patient changes from supine into standing position). These 2 effects are considered deleterious as they result in increased myocardial oxygen requirement.

In a nutshell, Nitroglycerin (GTN) causes general vasodilation:

1. **Arteriolar dilation**: short lived (5-10 min). NTG decreases systemic blood pressure (afterload), initially. This can elicit the baroreceptor reflex to cause reflex tachycardia and increased contractility and might increase Myocardial Volume Oxygen (consumption).
2. **Venous dilation**: more intense, even with low doses (so it is more selective), lasts for 30 minutes. NTG decreases venous return (preload) and decreases MVO2.

- The table beside summarizes what we have already talked about. *(the professor read it)*

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

Well, now we will discuss the side effects that result from Nitroglycerin's usage

- Side Effects of Nitroglycerin:

1. Headache (due to the vasodilation of cerebral arteries)
2. Hypotension and tachycardia
3. Increased intraocular and intracranial pressures
4. Methemoglobinemia
5. Tolerance when chronically used => only for the arteriolar effects.
6. Withdrawal may causes symptoms of angina (pain & etc.). This was discovered in those who work at ammunition industry and usually are exposed to nitrates during their work. During weekends, these workers become unexposed to nitrates=> symptoms of angina arise.

Notice the different routes of administration that we can find for nitrates.

- Nitroglycerin may be given sublingually because this mode of administration avoids first - pass hepatic metabolism.

▶Can be administered by various routes.
▶Fast onset of action (1-3 minutes, peaks at 10 minutes).
▶Short duration (15-30 minutes).

The route of elimination is by reductase enzyme in the liver.

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

(The professor briefly went over them)

Beta Adrenergic Blockers

- Prevent actions of catecholamines, so they are more effective during exertion/stress (that is why they may be preferred=>young people).
- Do not dilate coronary arteries, might constrict them (since we have blocked beta-adrenergic receptors, alpha-receptors will have a higher chance to bind to epinephrine and NE).
- Do not increase collateral blood flow.
- Cause subjective and objective improvement:
  1. Decreased number of anginal episodes.
  2. Decreased Nitroglycerin consumption.
  3. Enhanced exercise tolerance.
  4. Improved ECG.

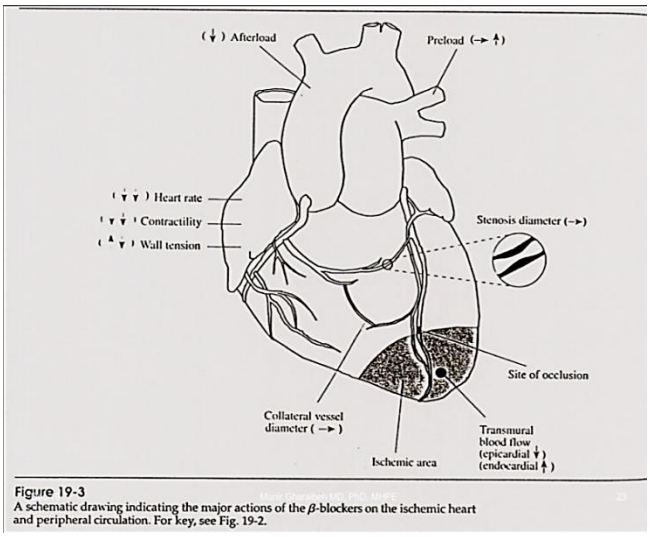


Figure 19-3
A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. For key, see Fig. 19-2.

Calcium Channel Blockers

- Particularly beneficial in vasospasm
- Can also affect platelets aggregation.
- May be dangerous in the presence of **heart failure** and in patients susceptible to **hypotension**.
- The figure below shows the chemical structures of several calcium channel-blocking drugs.

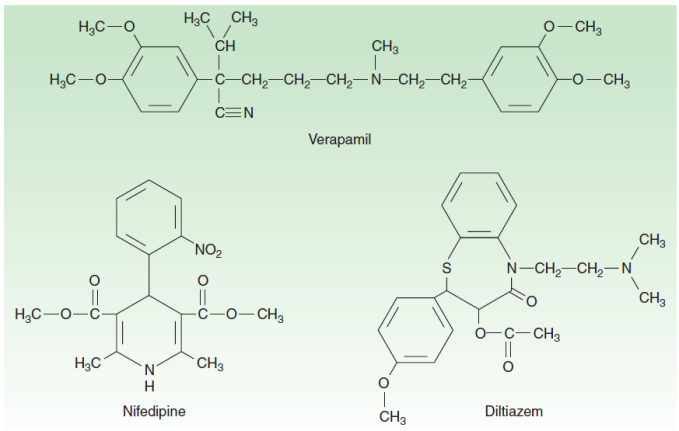
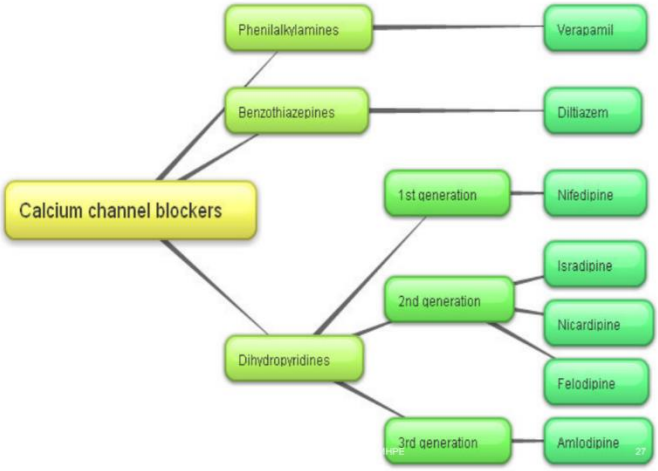


FIGURE 12–4 Chemical structures of several calcium channel-blocking drugs.

The figure beside lists the main calcium channel blockers.



Having said all of this, let us now talk about the properties of several recognized voltage-activated calcium channels.

The professor mentioned the first three types and their sites.

Notice that the calcium channel blockers that we have already mentioned act on type "L 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

The Effect of calcium channel blockers on our cardiovascular system is shown beside.

Notice that the drug's effect on the heart rate and contractility is variable (depends on the position of the patient).

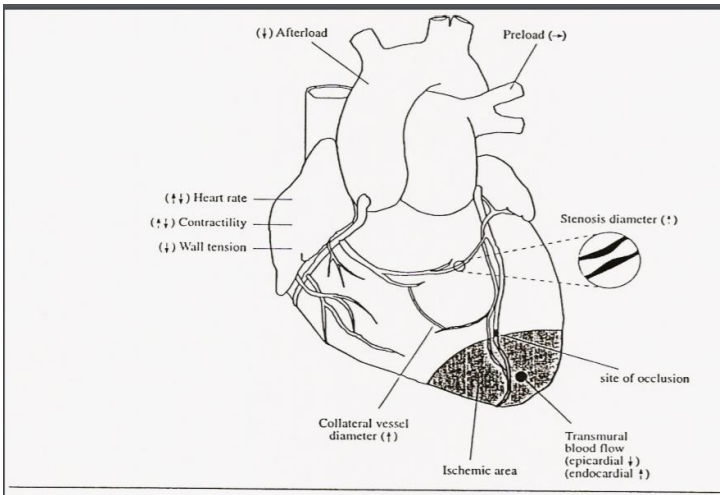


Figure 19-4
A schematic drawing indicating the major actions of the calcium antagonists on the ischemic heart and coronary circulation. For key, see Fig. 19-2.

Side effects of calcium channel blocker include:

1) Hypotension.
2) Headache.
3) Dizziness.
4) Flushing (especially in short acting drugs like Nifedipine).
5) Peripheral edema.

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

The table beside shows the effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.

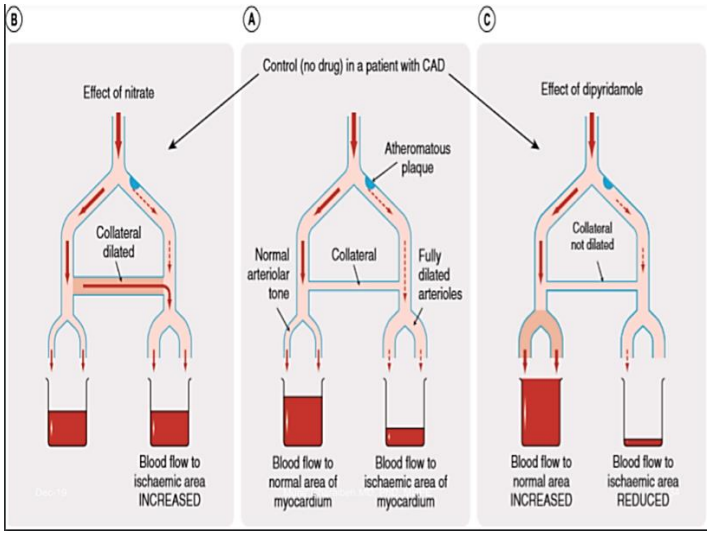
Make sure you understand it.

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

Dipyridamole

there is nothing much written about this drug in the slides. For further info refer to the last page in this sheet

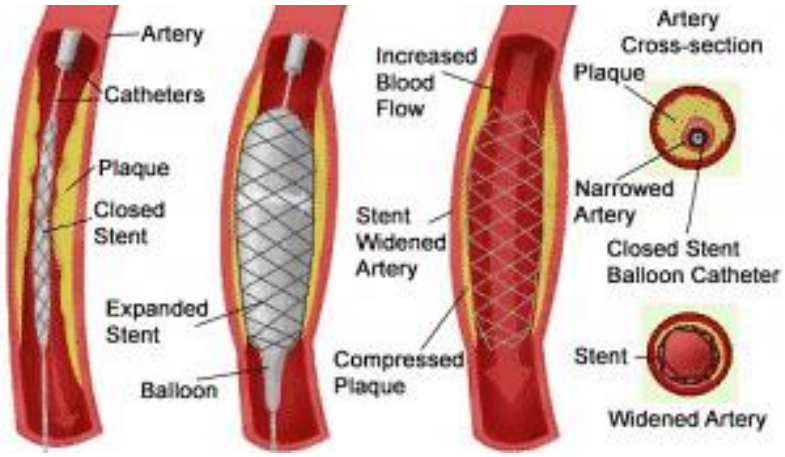
- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme
- **Thought** to be a good coronary dilator.
- Still used as an antiplatelet drug (in Transient ischemic attacks), but **not** better than aspirin. It could be given to patients who cannot tolerate aspirin due to gastric irritation.
- ncreases the blood flow to the **normal** area i.e. "Coronary Steal Phenomenon" as shown **beside**.



Therefore, nitrates pre-treatment can be used. Nitrates increase coronary blood flow to ischemic areas by supporting that epicardial vessel dilation.

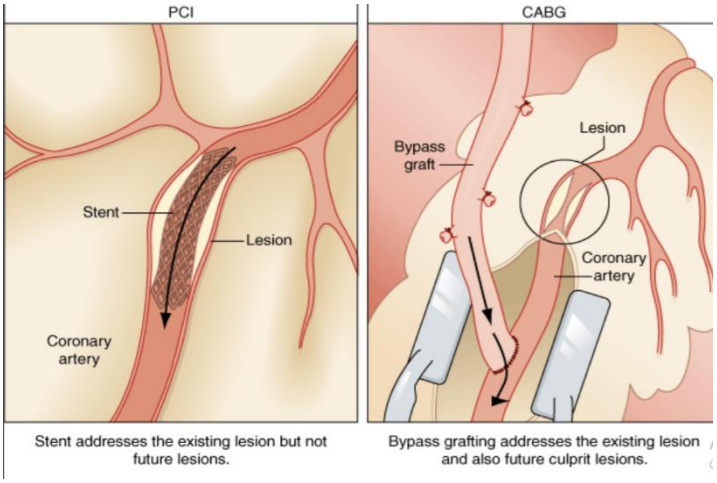
Other agents that are used to treat Angina include:

- Angiotensin converting-enzyme inhibitor (ACEI)
- Anticoagulants and/or Thrombolytic Therapy
- Cholesterol Lowering Agents (They have anti-inflammatory effect)
- Surgery
- **Angioplasty** (the procedure is shown in the figure below)



Extra

Percutaneous Coronary Intervention (**PCI**, formerly known as angioplasty with stent) is a non-**surgical procedure** that uses a catheter (a thin flexible tube) to place a small structure called a stent to open up blood vessels in the heart that have been narrowed by plaque build-up, a condition known as atherosclerosis.



Coronary artery bypass grafting (CABG) is a type of surgery that improves blood flow to the heart. It's used for people who have severe coronary heart disease (CHD).

Newer Antianginal Drugs **in the slides but not mentioned by the professor**

- 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

Extra:

Special Coronary Vasodilators

Many vasodilators can be shown to increase coronary flow in the absence of atherosclerotic disease. These include **dipyridamole** and **adenosine.** In fact, dipyridamole is an extremely effective coronary dilator, but it is not effective in angina because of coronary steal (see below). Adenosine, the naturally occurring nucleoside, acts on specific membrane-bound receptors, including at least four subtypes (A1, A2A, A2B, and A3). Adenosine, acting on A2A receptors, causes a very brief but marked dilation of the coronary resistance vessels and has been used as a drug to measure maximum coronary flow **("fractional flow reserve," FFR)** in patients with coronary disease. The drug also markedly slows or blocks atrioventricular (AV) conduction in the heart and is used to convert AV nodal tachycardias to normal sinus rhythm.

Regadenoson is a selective A2A agonist and has been developed for use in stress testing in suspected coronary artery disease and for imaging the coronary circulation. It appears to have a better benefit-to-risk ratio than adenosine in these applications. Similar A2A agonists (binodenoson, apadenoson) are investigational. Adenosine receptor ligands are also under investigation for anti-inflammatory and antinociceptive and other neurological applications.

Coronary steal is the term given to the action of nonselective
coronary arteriolar dilators in patients with partial obstruction of a portion of the coronary vasculature. It results from the fact that in the absence of drugs, arterioles in ischemic areas of the myocardium are usually maximally dilated as a result of local control factors, whereas the resistant vessels in well-perfused regions are capable of further dilation in response to exercise. If a potent arteriolar dilator is administered, only the vessels in the well perfused regions are capable of further dilation, so more flow is diverted ("stolen") from the ischemic region into the normal region. Dipyridamole, which acts in part by inhibiting adenosine uptake, typically produces this effect in patients with angina. In patients with unstable angina, transient coronary steal may precipitate a myocardial infarction. Adenosine and Regadenoson are labelled with warnings of this effect.

CASE STUDY ANSWER

The case described is typical of coronary artery disease in a patient with hyperlipidaemia. Her hyperlipidaemia should be treated vigorously to slow progression of, and if possible, reverse, the coronary lesions that are present *Coronary angiography* is not indicated unless symptoms become much more frequent and severe; revascularization may then be considered. Medical treatment of her acute episodes of angina should include sublingual tablets or sublingual **Nitroglycerin** spray 0.4–0.6 mg. Relief of discomfort within 2–4 minutes can be expected. To prevent episodes of angina, a **β blocker** such as metoprolol should be tried first. If contraindications to the use of a β blocker are present, a medium- to long-acting **calcium channel blocker** such as verapamil, diltiazem, or amlodipine is likely to be effective. Because of this patient's family history, an antiplatelet drug such as low-dose **aspirin** is indicated. Careful follow-up is mandatory with repeat lipid panels, repeat dietary counselling, and lipid-lowering therapy.

Lecture notes

Angina occurs when oxygen delivery to the heart is inadequate for myocardial requirement.

1) Stable / classic angina (angina of effort or exercise) is due to coronary atherosclerotic occlusion.
2) Vasospastic or variant angina (Prinzmetal) is due to a reversible decrease in coronary blood flow.

Treating stable and vasospastic angina involve:

1. INCREASING oxygen delivery by ↓ vasospasm. How? → Nitrates and CCBs.
2. DECREASING oxygen requirement by ↓TPR, ↓CO, or both. How? →Nitrates, CCBs, and beta blockers.

*Nitrates (prodrugs of nitric oxide)

- MOA: Vasodilation (venodilation, mainly) ⤵
  ↓preload → ↓cardiac work → ↓ oxygen demand
- Side effects:
  Flushing, headache, hypotension (orthostatic; caused by an upright posture).
- Associated with reflex tachycardia and fluid retention ☹

**Calcium channel blockers

- Beneficial in treating vasospastic angina.
- Can affect platelets aggregation.
- Dangerous in the presence of heart failure and in patients susceptible to hypotension

***Beta blockers

- Beneficial in treating stable angina.
- Do not increase collateral blood flow.
- Do not dilate coronary arteries, might constrict them.
- Contraindicated in vasospastic angina.

Good Luck!!