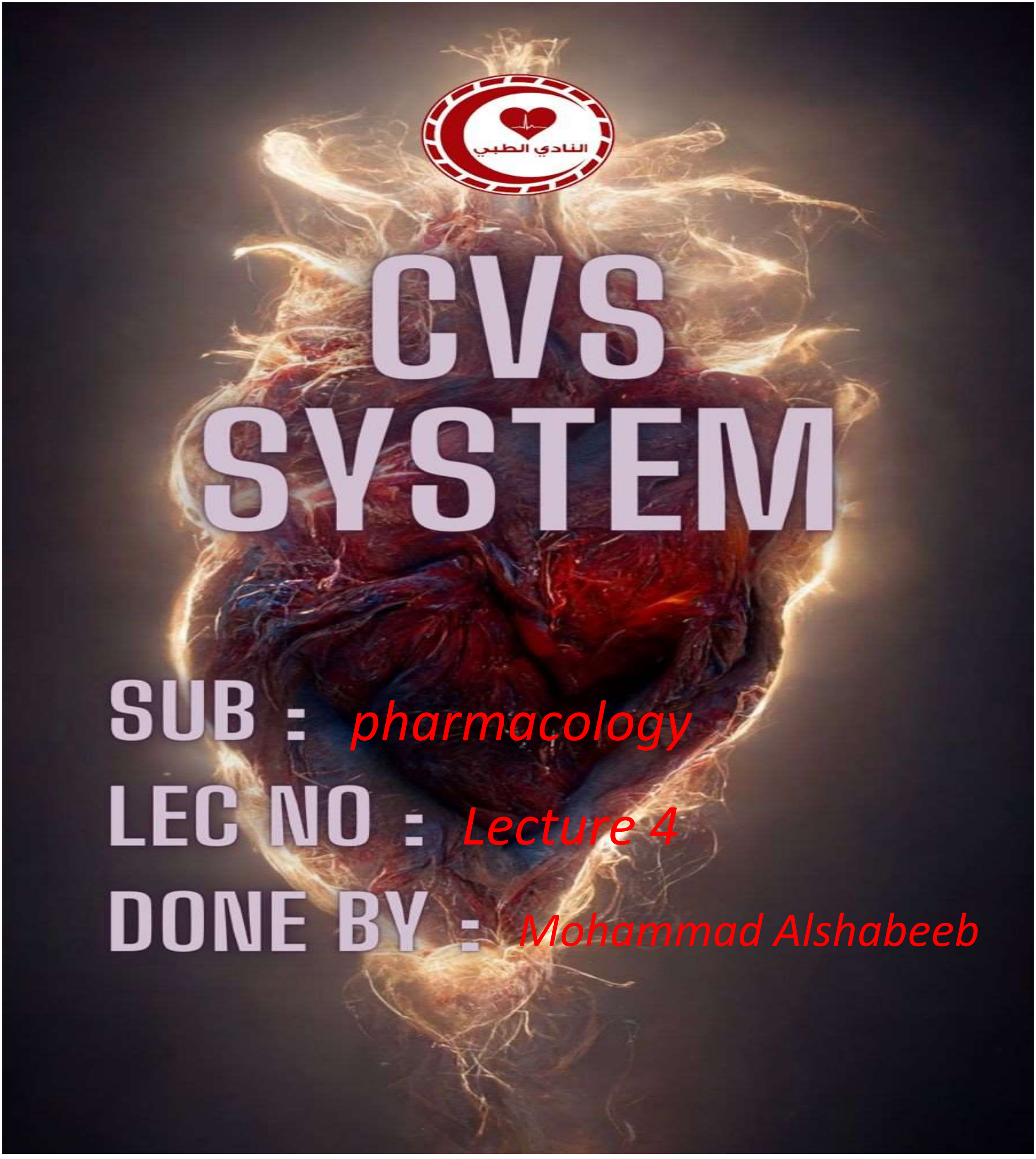
النادي الطبي
CVS
SYSTEM
SUB : pharmacology
LEC NO : Lecture 4
DONE BY : Mohammad Alshabeeb

CVS- Pharmacology 4

Antianginal drugs 1

Faculty of Medicine

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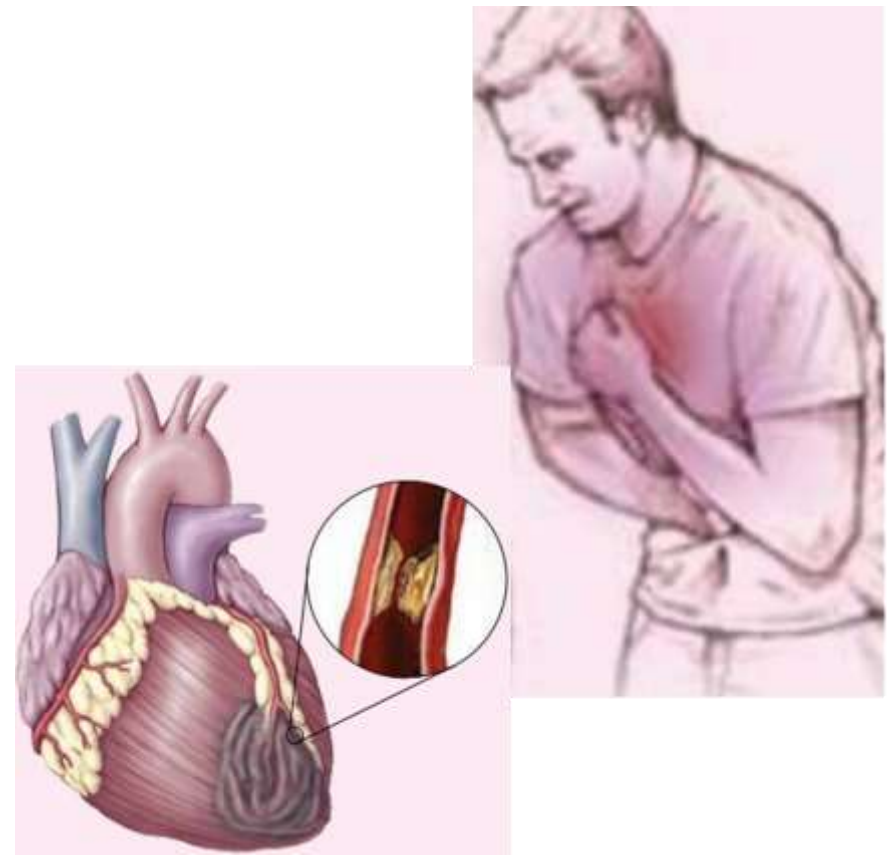
Angina

Chest pain or discomfort occurs when some part of the heart muscle **does not get enough blood supply**.

Patients may describe it as an intense pressure or a squeezing pain in their chest. The pain may radiate to the **shoulders, arms, neck, jaw, or back.**

هاي ال symptoms بتكون عند الناس ال non diabetic لكن عند الناس ال diabetic and women بتكون مش كلاسيك مثل الم في الايد وبكونوا hard to diagnosed



Fat deposition: plaque in coronary artery

Risk Factors: هاي ال risk factor احفظوهم

•Elevated LDL-cholesterol, age, cigarette smoking; high blood pressure, sedentary lifestyle, obesity, type 2 diabetes.

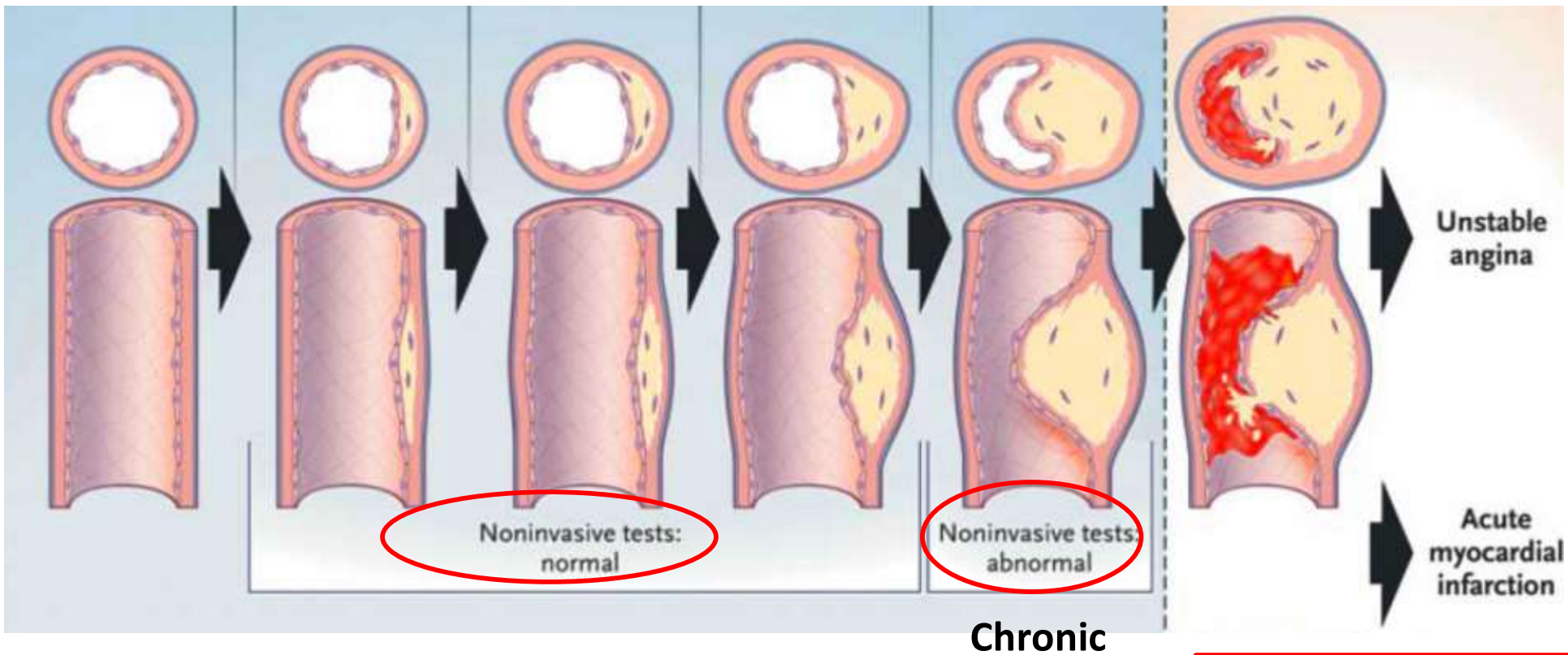
Occurrence: Its very common

•About 6 million Americans suffer from chronic angina

•About 400,000 new cases are reported each year

Progression of Coronary Atherosclerosis

Normal | Fatty streak | Plaque | Increasing Plaque | **Obstructive Athero-sclerotic Plaque** | Plaque fissure results in thrombosis



Chronic Stable Angina

Unstable angina

Acute Myo-cardial Infarction

If a thrombus (clot) completely occludes the coronary artery for a sufficient period of time, the downstream cardiac tissue may become infarcted (a necrotic lesion may form), leading to an **acute myocardial infarction** (AMI).

Types of Angina

Chronic stable angina, also called 'angina of effort' and 'exertional angina', is the most common form and is a result of coronary artery disease.

More common

Unstable angina is caused by the rupture of an atherosclerotic plaque. Chest pain is felt in the absence of exertion due to blockage of a coronary artery. At rest

Coronary Artery Spasm (aka Variant angina; aka Prinzmetal's Angina) is caused by contraction of smooth muscles in the wall of a coronary artery that leads to narrowing of the vessel and obstruction of blood flow. This is a **rare condition**.

Spontaneous Coronary Artery Dissection (SCAD) occurs when a tear or rupture forms in one of the coronary arteries, slowing or blocking blood flow to the heart. This is a **rare condition**.

Types of Angina:
Chronic stable angina is also called angina of effort; intense pain is associated with exercise, and the classical example is walking up a flight of stairs.
Over time, the plaque may increase in size and the fibrous cap may rupture, giving rise to unstable angina. Pain is felt even in absence of exertion and may signal an impending heart attack.
There is a third type, which I will not discuss in depth, called variant angina. It is relatively rare and accounts for ~2% of all cases of angina. It is not caused by athereosclerotic plaque. Rather, vasospasm due to contraction of the smooth muscles of the artery narrows the artery and reduces blood flow. Cause is not known, and is generally treated with nitrates. Pain is not associated with exercise.

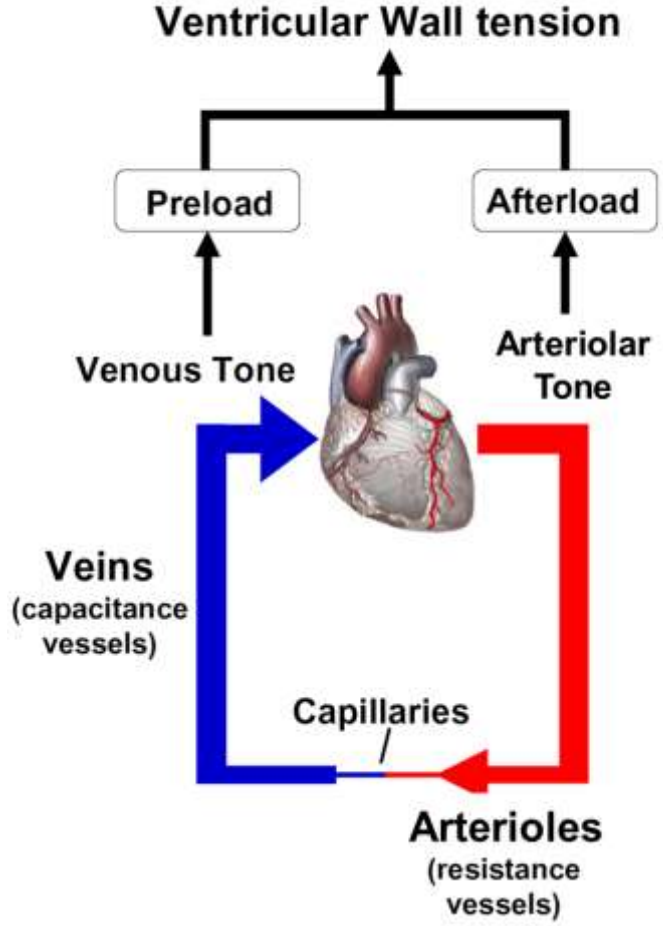
Major Determinants of Myocardial Oxygen Consumption

1. Doubling **heart rate** approximately doubles O_2 consumption; كل ما زاد ال heart rate بزيد الطلب عال اوكسجين وهاي بتصير بحالات ال , exercise وال stress

2. Increasing **contractility** increases O_2 consumption.

3. Increasing **afterload**, due to the increase in tension development (ventricle must work harder to eject blood). لانه رح تزبد ال resistance فبالتالي رح ابذل مجهود اكثر

4. Increasing **preload** (ventricular end-diastolic volume), because the ventricle is forced to contract against a larger volume, resulting in increased ventricular wall tension. لانه بكون في عندي كمية دم كبيرة بال end diastolic volume فبالتالي انا لازم اضخ دم اكثر ف رح استهلك اوكسجين اكثر



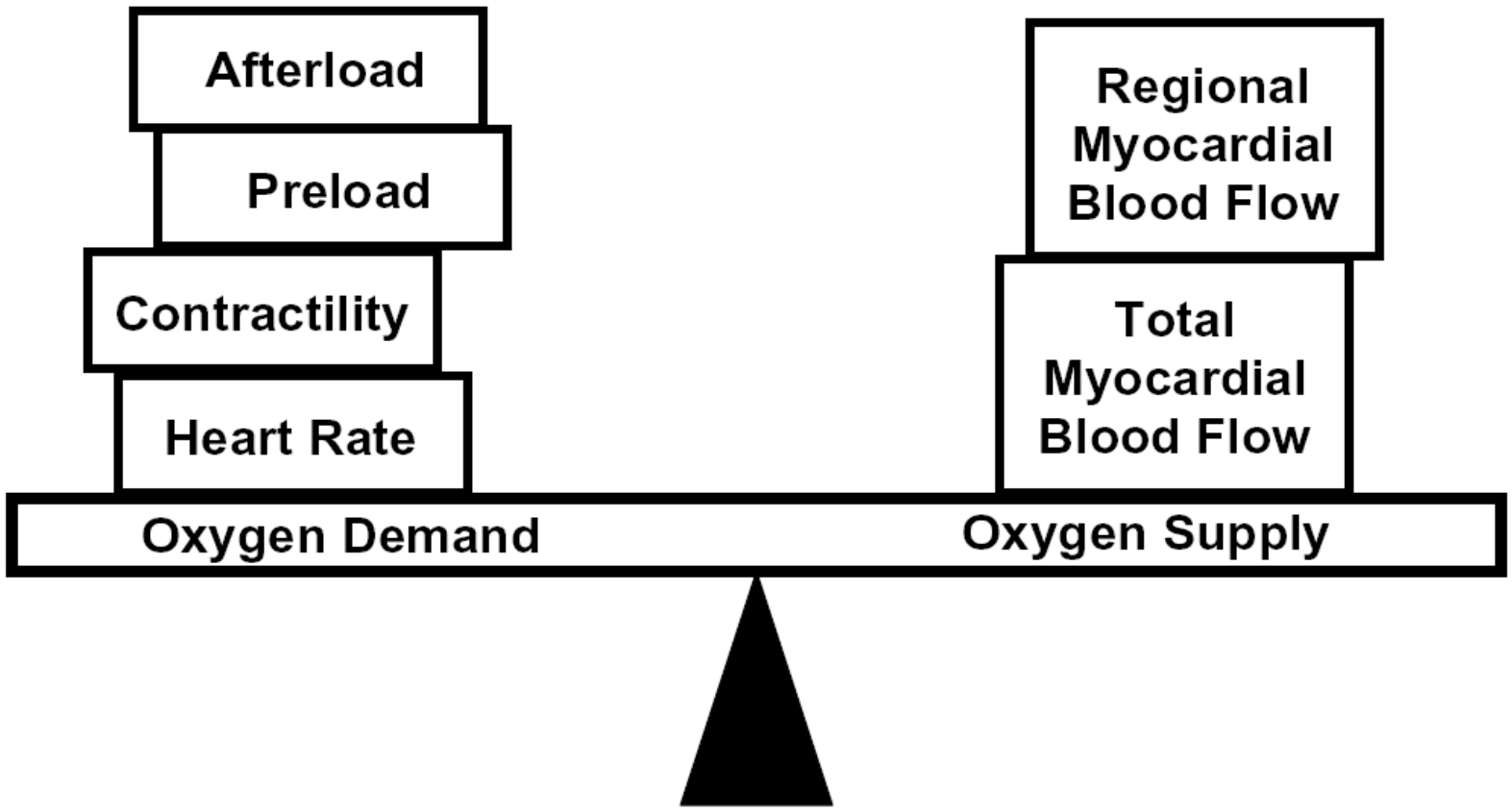
فعشان هيك انا اذا بدي اعطي treatment لازم اقلل وحدة منهم
ليش؟ لانه اذا قللت استهلاك الاوكسجين رح احتاج less blood
supplyوهيك بقلل من ال symptoms of angina

With an increase in preload, the cardiomyocytes contract with greater force (Frank-Starling mechanism) and eject a larger volume of blood. This requires more work and oxygen demand increases.

With an increase in afterload, there is an increase in left ventricle pressure development during isovolumetric contraction (in order to overcome the greater peripheral resistance).

With an increase in contractility, there is an increase in actin-myosin cross-bridges, which increases the velocity and force of muscle fiber shortening. This leads to a greater ejection fraction and larger stroke volume, but also increases oxygen demand

In a Healthy Heart, Oxygen Supply is in Balance with Oxygen Demand

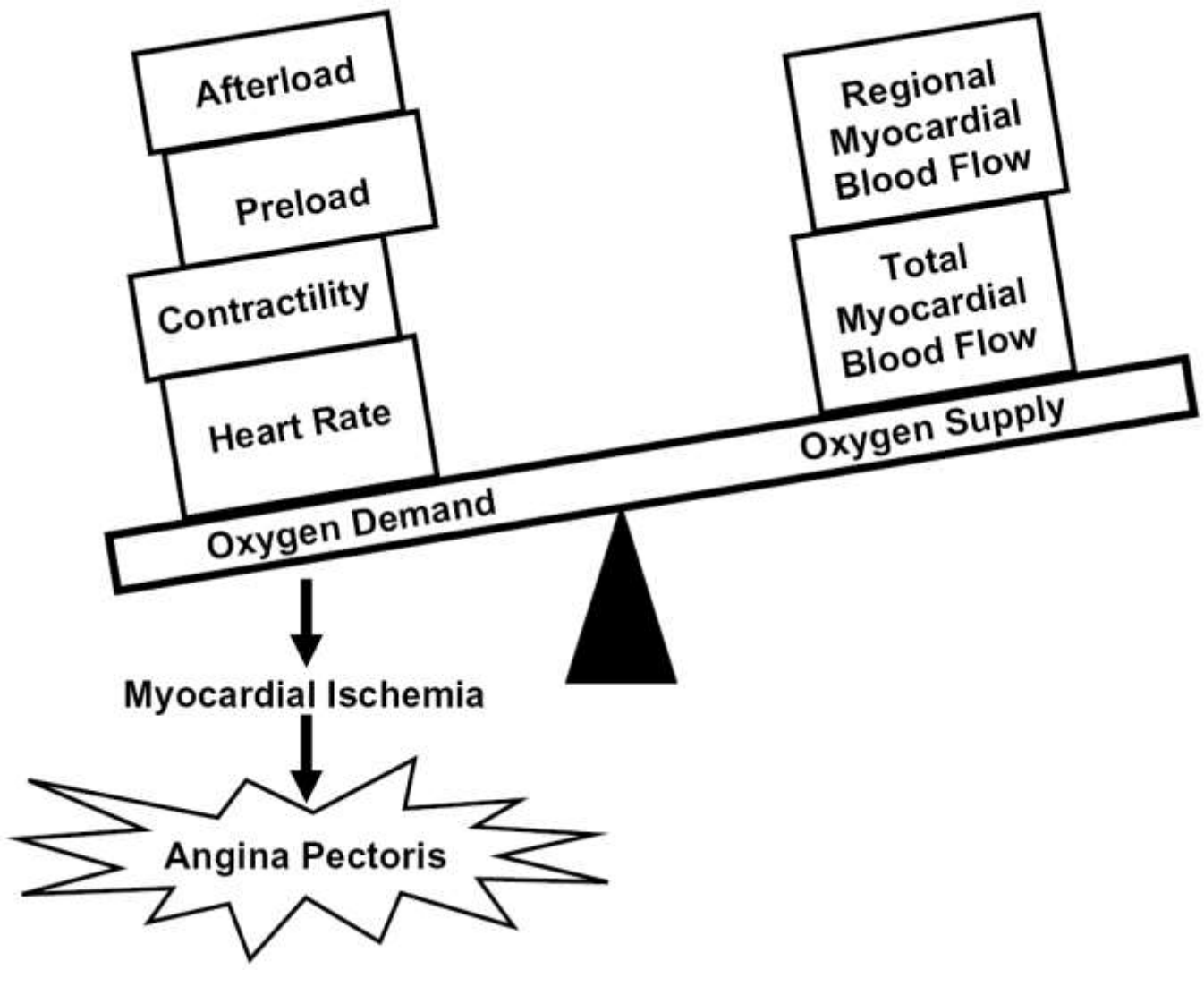


Total blood flow is measured in the left coronary artery

Regional and total myocardial blood flow can be determined using positron emission tomography. Regional flow refers to flow downstream of stenosis; i.e. flow to a specific region, or territory of the heart supplied by an artery.

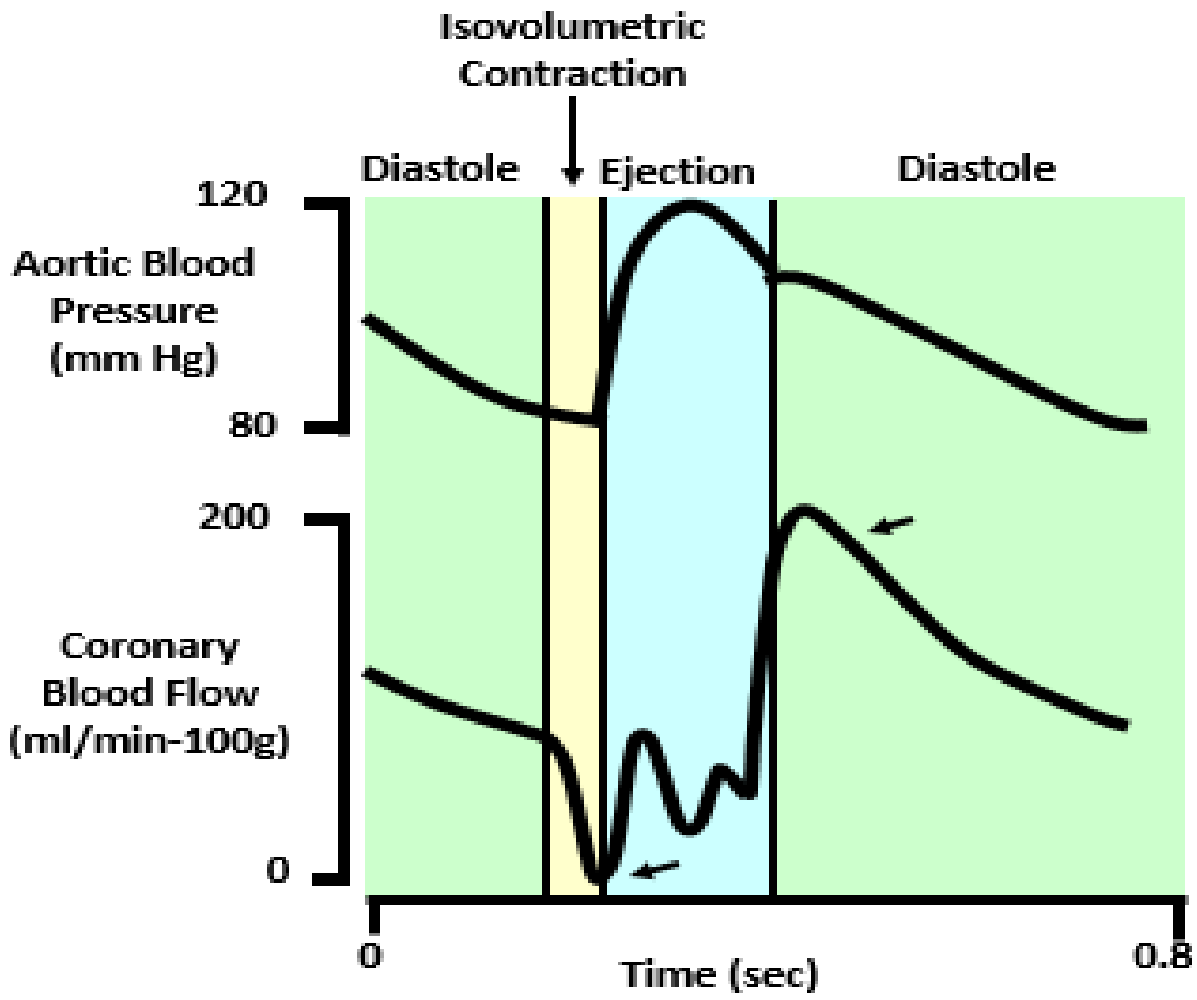
Normally supply and demand are in balance. If you run up a flight of stairs, oxygen demand increases, and coronary vessels dilate to supply more blood to the myocardium. As we will see, in cases of angina pectoris, regional blood flow may be inadequate during exercise. That is, the subendocardial vessels may not be able to supply enough blood to meet the increased oxygen demand.

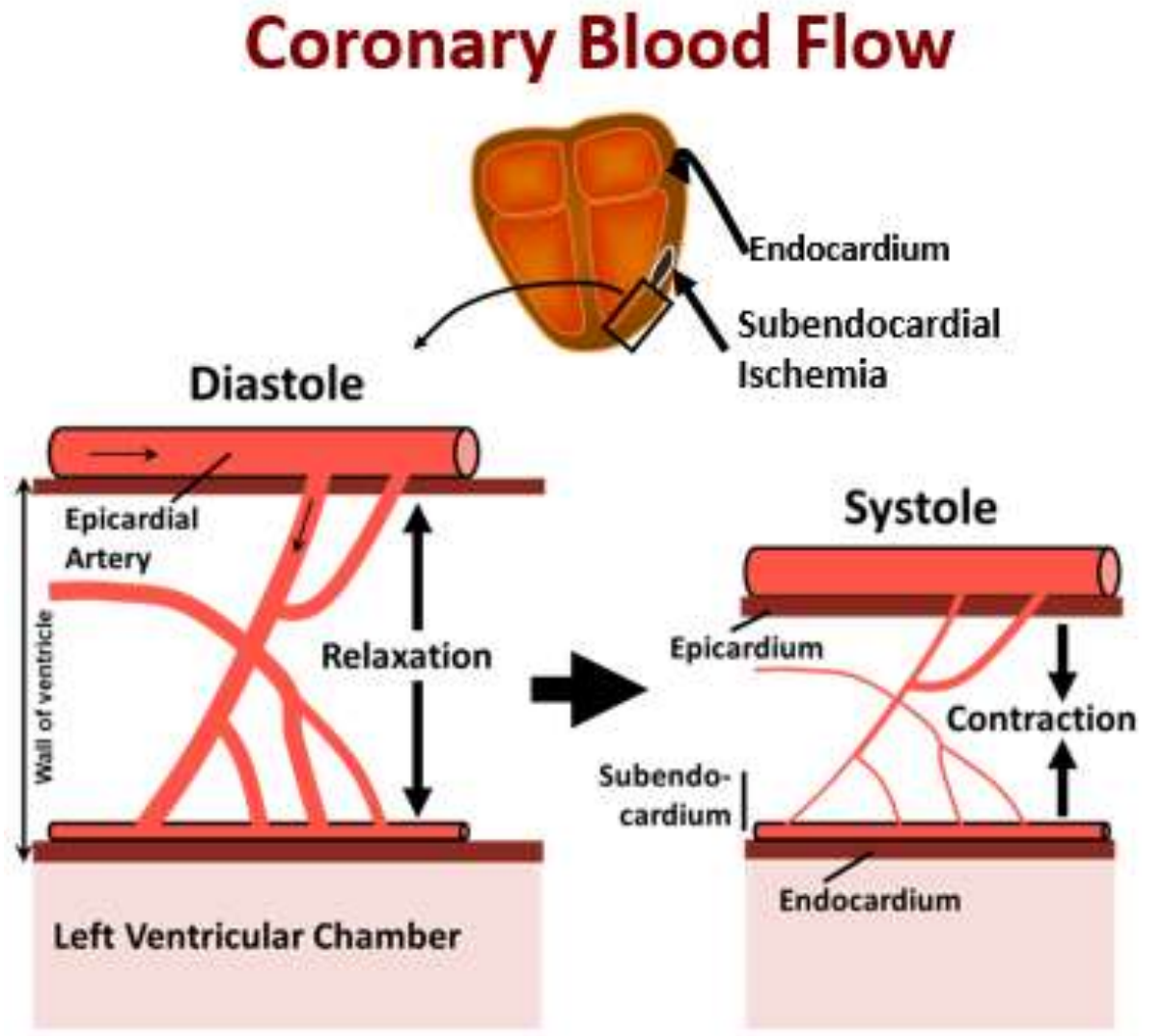
Angina Results From an Imbalance Between Oxygen Supply and Demand



هسا احنا بالوضع الطبيعي عندنا balance between
oxygen demand and oxygen supply لكن اذا صار
عندي خلل يهذا التوازن مثلا زاد ال demand رح يأدي ل
myocardial ischemia و angina pectoris وربما اذا
طولت بتأدي الى MI

Coronary Blood Flow





هان بدك تعرف انه ال maximal blood flow in the coronary artery بكون في ال early diastole

Coronary blood flow here is in reference to the subendocardial region. As can be seen, flow essentially ceases for a brief period as the ventricle contracts. The left and right coronary arteries originate at the base of the aorta, just past the aortic valve. So as blood is ejected from the left ventricle, it is forced into the left and right coronary arteries. Note that coronary blood flow does not peak until diastole.

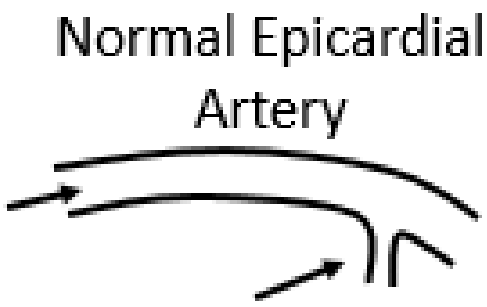
في منطقة بال heart نسميها endocardium هاي كثير مهمة يمكن اذا يصير عندي contraction هي اكثر منطقة يتعتمد على ال vessels الصغيرة اللي هم branch of coronary artery to blood supply فهاي بالعادة بتكون susceptible انه يصير فيها ischemia ف بحالة ال diastole بكون فيها relaxation and more blood flow to this اما في حالة ال systole كمية الدم بتكون اقل

As oxygen demand increases, as with exercise, the subendocardial vessels dilate (in response to local metabolic factors such as adenosine nitric oxide) to maintain adequate perfusion. The nerves of the heart can be removed and still there is a response of dilation to increased oxygen demand.

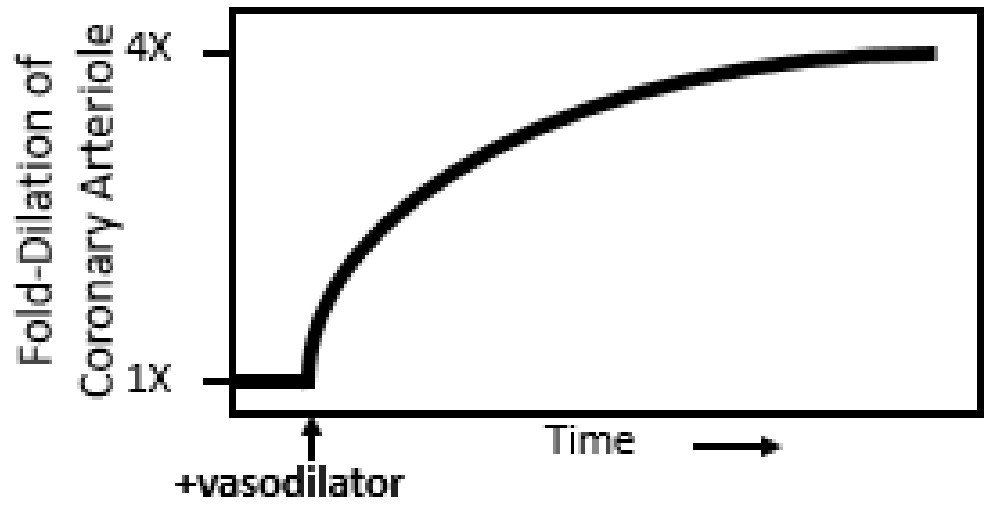
Note that occlusion of an epicardial artery is particularly problematic for the subendocardial vessels. If the epicardial vessels are occluded by ~80%, then the subendocardial vessels are fully dilated even at rest. Upon exercise, no further dilation can be achieved, and the demand for oxygen is not met, resulting in angina.

Here I'm showing a simple diagram of the coronary flow patters, but blood flow can be measured during the cardiac cycle. (NEXT SLIDE).

Coronary Flow Reserve

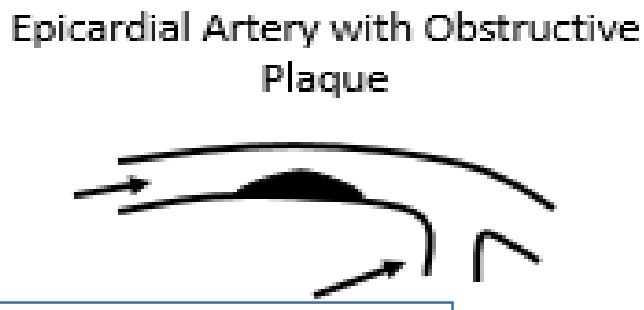


Arteriole can dilate upon exertion, or if a vasodilator is administered

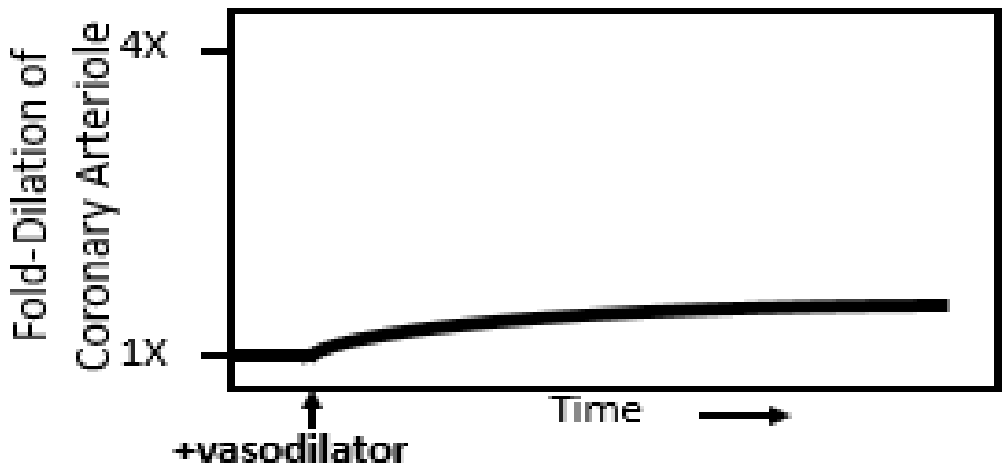


هسا انا لما بحتاج o2 الجسم بفرز local chemical such
فبزيد ال blood (NO) that promote vasodilation
والـ o2 supply

Coronary flow reserve relates to the ability of the coronary arterioles to dilate and **increase blood supply to the heart.** Coronary flow can be thought of as a **'safety margin'.**



Arteriole in **ischemic region is maximally dilated** and is unable to dilate further upon exertion, or when a vasodilator is administered.



اما بالحالات لما يكون عندي اصلا obstruction ف انا
بهاي الحالة حتى at rest انا بكون مفرز NO وبكون عندي
vasodilation ف لما احتاج اكثر اوكسجين ما رح اقدر
اعمل vasodilation كافي لانه بالاصل متوسعات

With obstructive plaque, the coronary arterioles in the ischemic region are fully dilated even at rest in order to supply sufficient blood to the heart muscle. This means there is very little safety margin if oxygen demand increases (as with exercise).

Coronary flow reserve relates to the ability of the coronary arterioles to dilate and increase blood supply. Coronary flow can be thought of as a kind of safety margin.

With obstructive plaque, the arterioles are fully dilated even at rest in order to supply sufficient blood to the heart muscle. This means there is very little safety margin if oxygen demand increases (as with exercise).

Lines of Treatment

1. General measures:

بعالج الاعراض وال comorbidity

- **Manage comorbidities** such as hypertension (diuretics), dyslipidemia (statins), thrombosis, and type 2 diabetes.
- **Associated conditions** as anemia, valvular heart disease should be corrected .

هسا هاي الطرق اللي بعالج فيها ال Angina لكن احنا رح نتحدث بشكل رئيسي عن نقطة 2

2. **Antianginal** drugs.

3. Other measures: **PCA** (Percutaneous coronary angioplasty), **Grafting** (Aorto-coronary bypass grafting), **Aspirin 75 mg daily indefinitely**

Drugs for Chronic Stable Angina

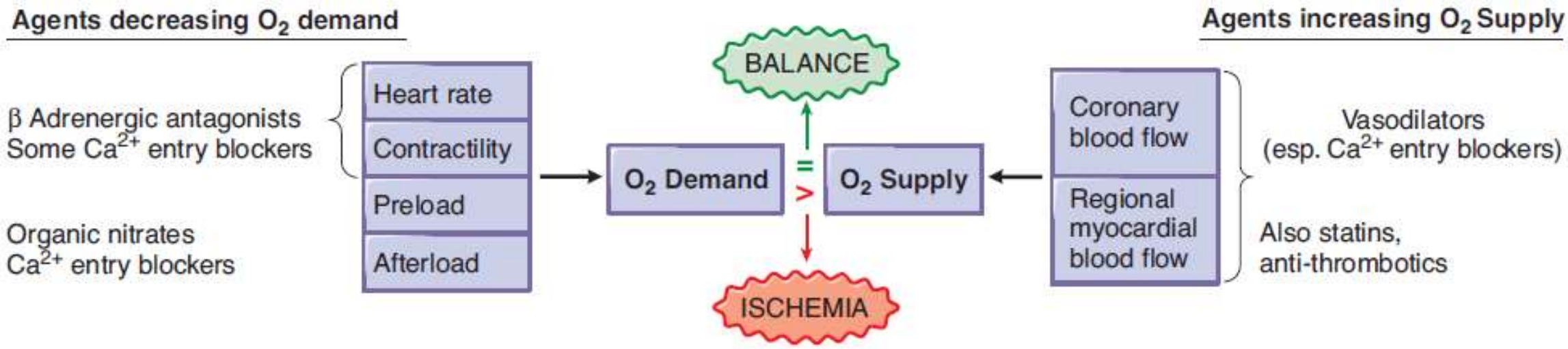
Antianginal drugs are used **to relieve the symptoms of pain/discomfort associated** with cardiac ischemia by restoring the balance between oxygen supply and demand.

هسا احنا رح نستخدم هاي الادوية لنتحكم بال heart rate , contractility ,preload , afterload

1. **Beta-Blockers**
2. **Calcium Channel Blockers (CCBs)**

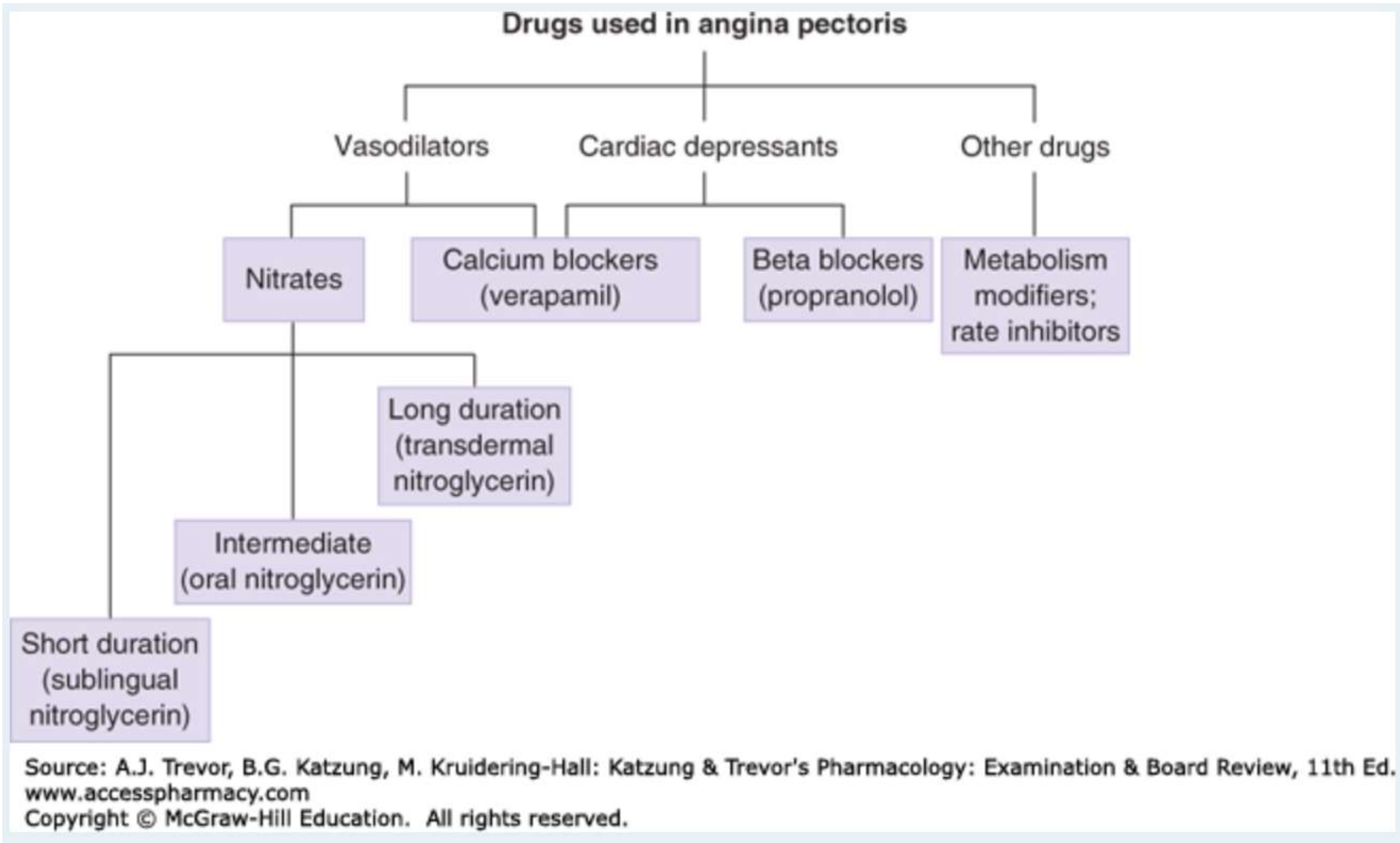
اليوم رح نحكي عن اول 2

3. **Organic nitrates**
4. **Newer antianginal drugs**: Ranolazine

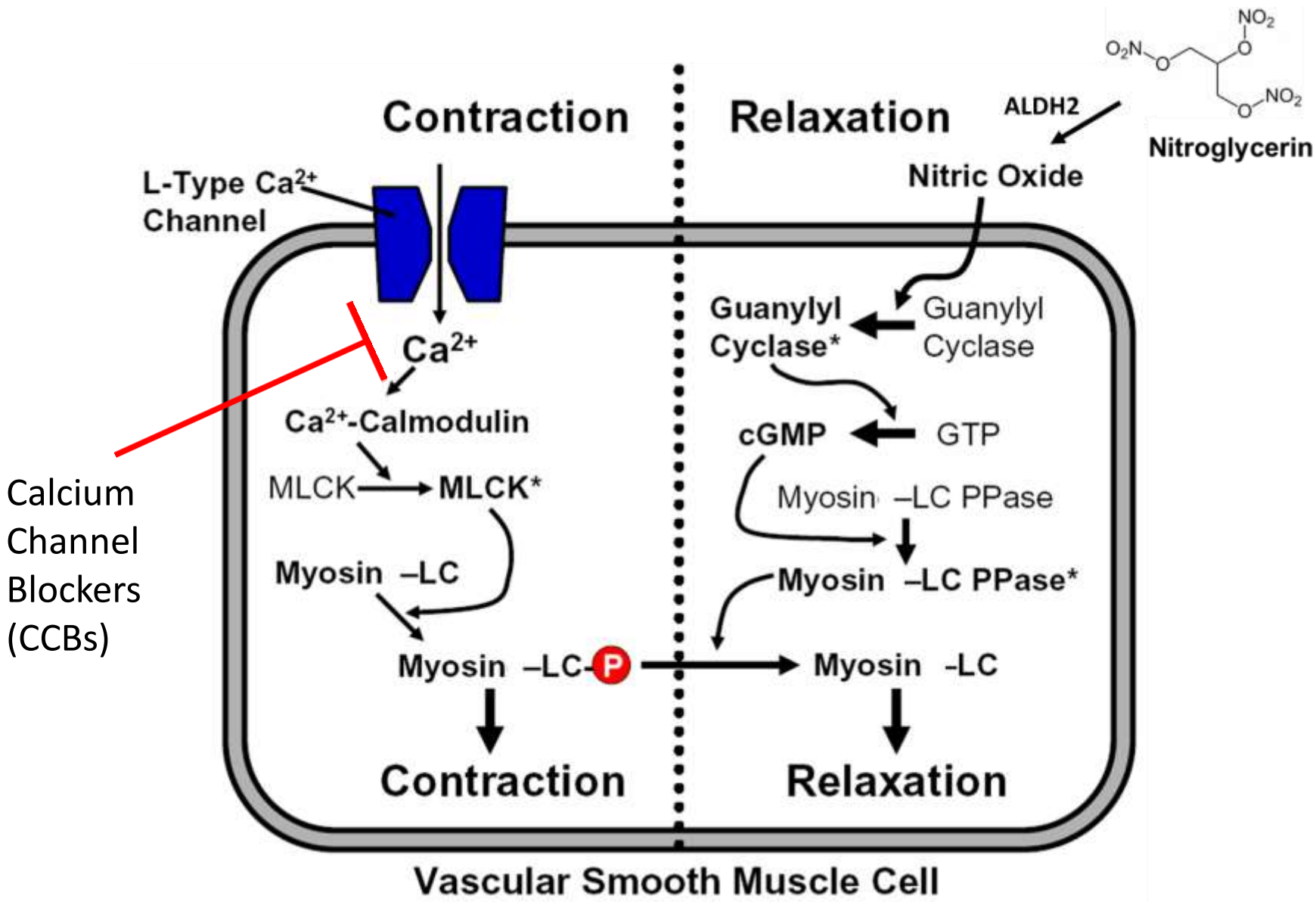


هسا انا هدفي الرئيسي اني اعمل balance between
فعشان هيك انا بدي ادوية o2 demand and supply
تعمل وحدة من الاثنين اما يتزيدلي من ال o2 supply او
يطريقة معينة o2 demand بتقللي من ال

Drugs for Chronic Stable Angina



Drugs for Chronic Stable Angina



هسا ركزوا معاي بهالجملتين

انا عندي ال calcium channel blockers هاي بتمنع دخول الكالسيوم ف بتمنع ال contraction

وعندي كمان ال nitric oxide انا بقدر استعمله ك دواء
(nitroglycerin) ف هاذ بمنع ال dephosphorelation لل myosin فبعمل relaxation

Beta-Blockers

Beta-Blockers

- β1- receptors are located mainly in the **heart**. While β2-receptors are located mostly in **lung** and blood vessel cells, though heart cells also have some.
- The prototypical drug in the group is **Propranolol**, a non-selective beta-blocker (may cause bronchospasm due to block of β_2 receptors)
- All β -blockers are nonselective at high doses and can inhibit β2 receptors
- Propranolol has been largely replaced by cardioselective Beta-blockers, such as atenolol, metoprolol.

هسا ال B1 بتشتغل بشكل رئيسي على ال heart اما ال B2 بتشتغل برضو على ال lung فعشان هيك يفضل اني استخدم selective drug specific to B1 reseptors

- All β -blockers are nonselective at high doses and can inhibit β2 receptors

شرح هاي النقطة : انه كل ال B-blockers سواء بتشتغل على ال B1 or B2 اذا استخدمنا بجرعة عالية رح تشتغل على ال B2 فعشان هيك احنا لازم نكون caution لما نعطيهم لمريض asthma and diabetic فهما مش ال drug of choice لهذول المرضى

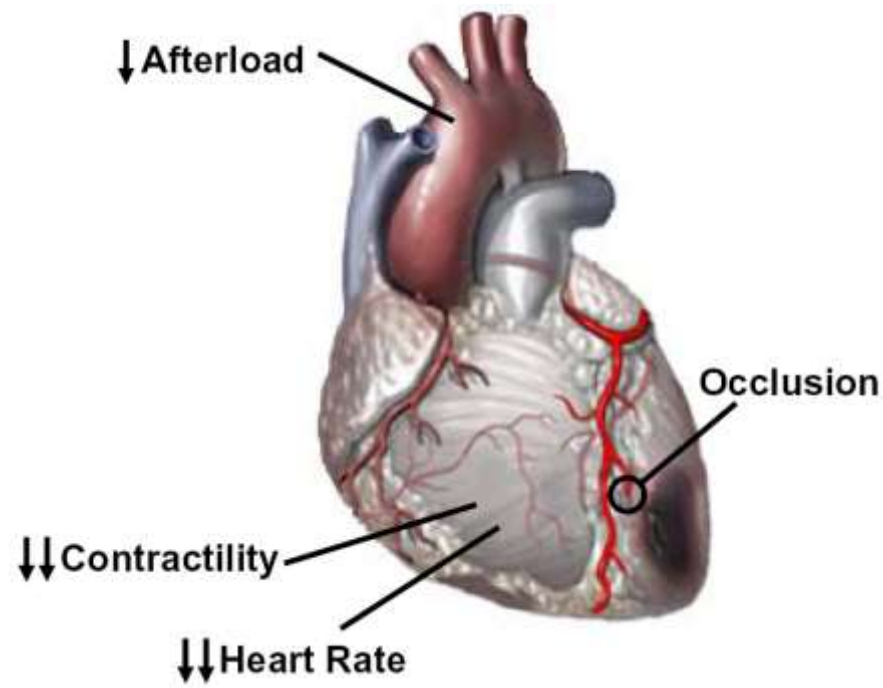
Beta-Blockers

- Beta-blockers are also used in the management of heart failure**, and** hypertension cardiac arrhythmias

- Beta-blockers competitively **inhibit the action of norepinephrine and epinephrine**.

Beta-Blockers

• β1 blocker decreases the heart rate and contractility. Overall, **the workload on the heart is reduced, which also reduces oxygen consumption.**



•β_1 blockers decrease the release of renin by the kidneys, which reduces circulating Angiotensin II levels and **reduces afterload** (overall Beta blockers have very little effect on preload).

Preload is largely unchanged with a beta blocker

Beta-Blockers

- β -Blockers can **reduce both the frequency and severity of angina attacks.**
- β -Blockers can be **used to increase exercise duration and tolerance in patients with effort-induced angina.**
- β -Blockers are recommended as initial antianginal therapy *First line* in all patients unless contraindicated.
- β -Blockers reduce the risk of death and MI **in patients who have had a prior MI and also** improve mortality in patients with heart failure **with** reduced ejection fraction.

Beta-Blockers

- β -Blockers should be avoid in patients **with severe bradycardia**.

يعني واحد بتكون عندو ال heart rate اصلا قليلة فمش معقول
استخدم ال B-blockers

- β -Blockers can be used in patients with diabetes, peripheral vascular disease. and chronic obstructive pulmonary disease, as long as they are monitored closely.

ولازم نكون حذرين لما نعطيهم لهذول الناس

- When a non-selective beta-blocker is used, **bronchoconstriction can occur**. Therefore, non-selective beta-blockers are contraindicated in patients with asthma or chronic obstructive pulmonary disease.

وهاي شرحناها فوق بس بدي اوضح شغلة انه بالناس ال diabetic
اذا اعطيتهم B-blocker هذا رح يعمل mas; يعنس رح يبطل
يظهر ال symptoms اللي بتدلني انه صار معاه hypoglycemia

Side Effects of Beta-Blockers

و هذول سهلين ف افهموهمم من الشغل اللي بعمله ال B-blocker

- The common side effects of beta-blockers are extensions of their mechanisms of action and **include** bradycardia**,** reduced exercise capacity**,** hypotension**, and** atrioventicular (AV) nodal conduction block**.**

- It is important not to discontinue β -Blocker's therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, Ml, and hypertension **due to upregulation of receptors.**

هاي النقطة جدا مهمة , يعني انا لما اوقف ال B-blocker ما لازم اوقفه فجأة لازم بالتدريج

Calcium Channel Blockers

Calcium Channel Blockers (CCBs)

- Block the voltage gated L-type calcium channel primarily in **arteriolar smooth muscle cells and cardiac tissue.**

- CCBs fall into two broad classes (chemical structure) , the **dihydropyridines** and the **non-dihydropyridines.**

- **Amlodipine, Nifedipine, Verapamil, Diltiazem.**

هسا هذول ال 2 وين اخذناهم قبل ؟

اذا بتتذكروا كانوا class 4 antiarrhythmic drug

Calcium Channel Blockers (CCBs)

- Calcium is essential for muscular contraction. **Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces.** In turn, this promotes the activity of several ATP-consuming enzymes, thereby **depleting energy stores and worsening the ischemia.**

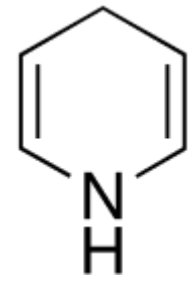
- The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are, therefore, arteriolar

- All calcium channel blockers lower blood pressure.

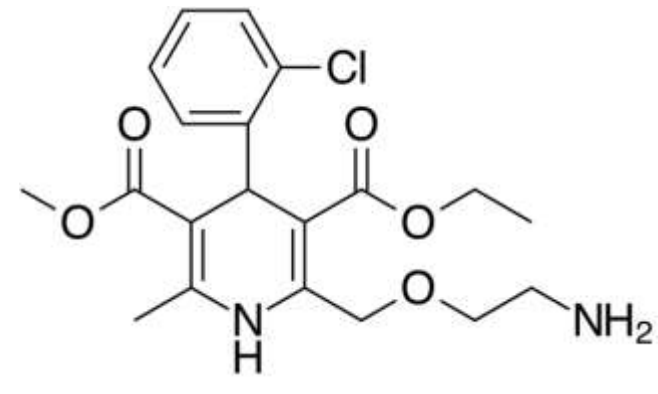
The dihydropyridines (CCBs)

Are more selective for vascular L-type calcium channels **primarily in arterioles**.

Amlodipine, **Nifedipine**.



Dihydropyridine ring

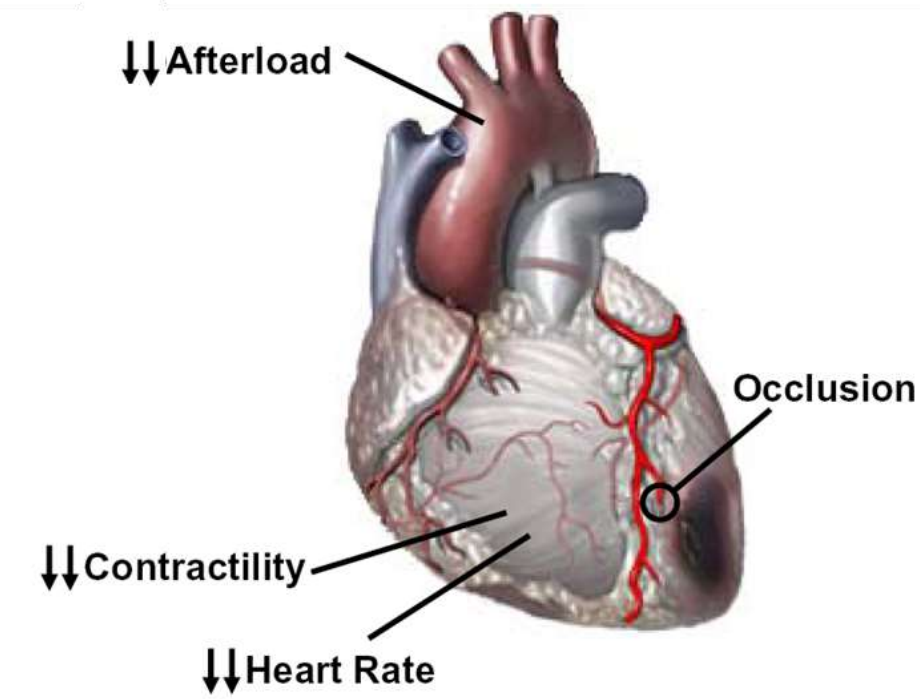


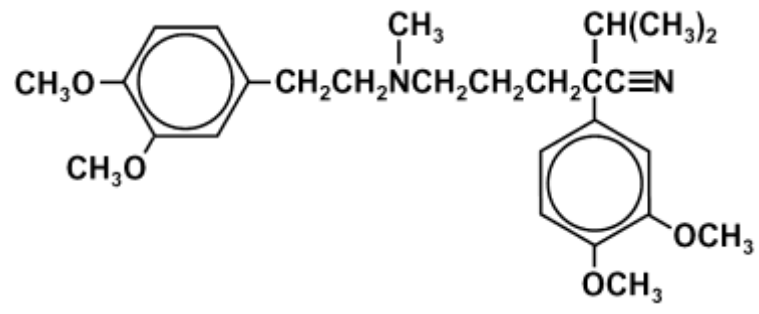
Amlodipine

afterload يعني اكثر شغله رح يكون على ال

Non-dihydropyridines Calcium Channel Blockers (CCBs)

- Relax vascular smooth muscle (causing vasodilation) which decrease the afterload.
- Decrease myocardial contractility.
- Decrease heart rate.
- **Verapamil**, **Diltiazem**.





Verapamil

Non-dihydropyridines Calcium Channel Blockers (CCBs)

وهان ابصموا

- *Verapamil* is contraindicated in patients **with preexisting depressed cardiac function or AV conduction abnormalities.**

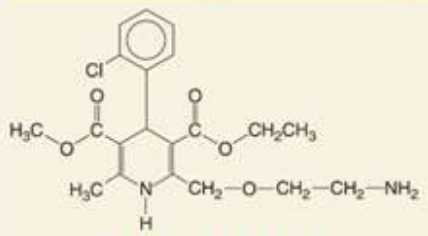
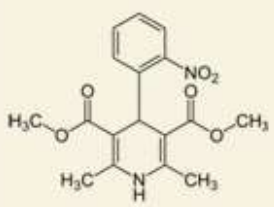
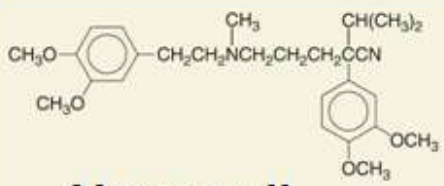
- *Diltiazem* also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator.

- Non-dihydropyridine calcium channel blockers **can worsen heart failure** due to their negative inotropic effect, and their use should be avoided in this population.

لانهم زي ما قلنا بقللوا من ال myocardial contractility وال heart rate

Table 27–2

Ca^{2+} Channel Blockers: Chemical Structures and Some Relative Cardiovascular Effects[a]

CHEMICAL STRUCTURE Generic name (trade name)	VASODILATION (ARTERIOLE FLOW)	SUPPRESSION OF CARDIAC CONTRACTILITY	SUPPRESSION OF AUTOMATICITY (SA NODE)	SUPPRESSION OF CONDUCTION (AV NODE)
 **Amlodipine**	5	1	1	0
 **Nifedipine**	5	1	1	0
 **Verapamil**	4	4	5	5

[a]Relative effects are ranked from *no effect* (0) to *prominent* (5). NR, not ranked. (Modified from Julian, 1987; Taira, 1987.)

Verapamil mainly affects the myocardium, whereas *amlodipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.]

Diltiazem is intermediate in its actions

Indications of Calcium Channel Blockers in Angina

- **Alternative** to **beta-blockers** in presence of **contraindications** to them.
- **With beta-blockers in resistant angina using nifedipine**
- **Prinzmetal's angina due to acute coronary spasm**

هان رح نحكي عنها بالمحضرة الجاي اكثر بس احنا لما نقلل دخول الكالسيوم بنقلل من ال spasm لل smooth muscles

Calcium channel blocker induced gum hypertrophy: no class distinction

A 49 year Afro-Caribbean man, with a 10 year history of resistant hypertension, was referred for further management on the following medications: amlodipine 20 mg, atenolol 200 mg, and enalapril 60 mg daily. Other treatments comprised: two-weekly modecate injections, procyclidine, and nocturnal temazepam 10 mg for stable schizophrenia. He had acquired a degree of renal impairment (creatinine clearance of 64 ml/min) as a result of his hypertension, but was not actively requiring dialysis. Pronounced gum hypertrophy with bleeding was a key initial clinical finding (below left). Withdrawal of the dihydropyridine calcium channel blocker resulted in slow regression of the gum hypertrophy. The blood pressure continued to be poorly controlled despite the use of six different antihypertensive drug classes (β blocker, α blocker, angiotensin II receptor blocker, potassium sparing diuretic as well as a loop diuretic, and a centrally acting agent). A non-dihydropyridine calcium channel blocker (diltiazem XL 240 mg daily) was therefore prescribed to try to improve the blood pressure. Unfortunately the gum features worsened again over a period of three months. They resolved several months after calcium channel blocker withdrawal (below right).

Gum hypertrophy is a well recognised side effect of dihydropyridine calcium channel blockers, with few reports following non-dihydropyridine calcium channel blockers. This case illustrates that it may occur with both major classes of calcium channel blockers and resolve following their cessation.

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Gum hypertrophy من ال symptoms لل calcium channel blocker وبكون reversible

With CCB

After withdrawal of CCB