

حالة مرضية تتمثل بقلّة وصول الدم والأكسجين للقلب : Angina

Antianginal Drugs

طيب كيف أصلاً أجزاء القلب بوصلها دم (تروية القلب)؟

عن طرق الـ coronary arteries (الشرايين التاجية) ولو لأي سبب من الأسباب قلت كمية الدم الواصلة للقلب

(أي جزء) بالإضافة لقلّة كمية الأكسجين الواصلة (hypoxia) فبصير عندي قلّة تروية (مش انقطاع كامل للدم)

← مهمة جداً
صاي العلوم

وبصير عندي ذبحة صدرية angina

طيب خايني احكي شوية عن موضوع الـ hypoxia ، قلّة الـ O2 بتخلي الخلية تسلك إحدى المسارات التالية :

١. بتوقف عن الشغل

٢. بتصير تشتغل anaerobic وهاد الحكي ينتج lactic acid وهاي المادة المسؤولة عن حدوث pain

(sudden, severe pain) وموقعه يكون بالـ (chest lift, arm and neck)

“Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms”

1

2

3

4

5

Coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to hypoxia

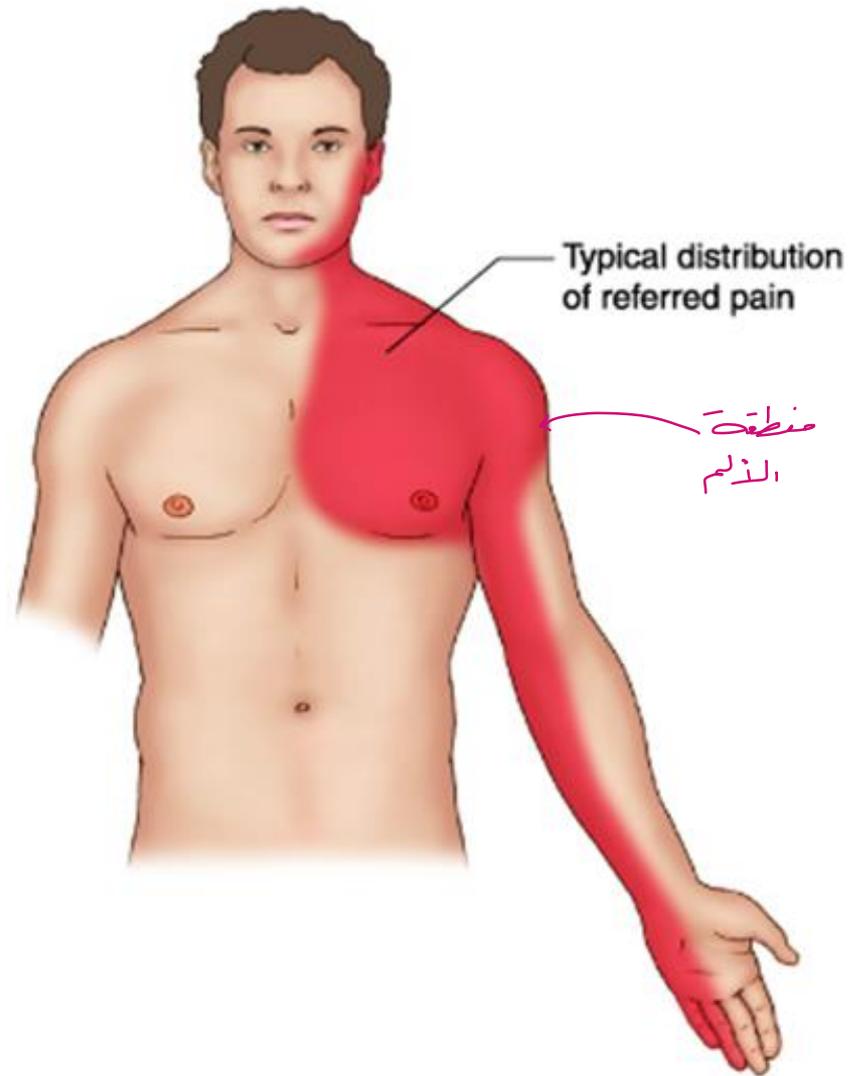
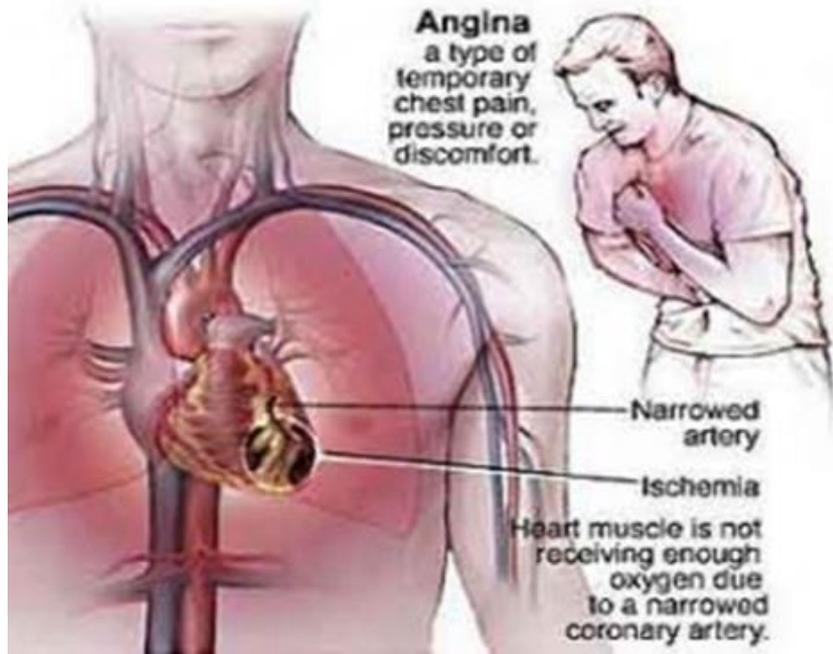
Oxygen demand

كمية الأكسجين المستهلكة لعمل عضلة القلب

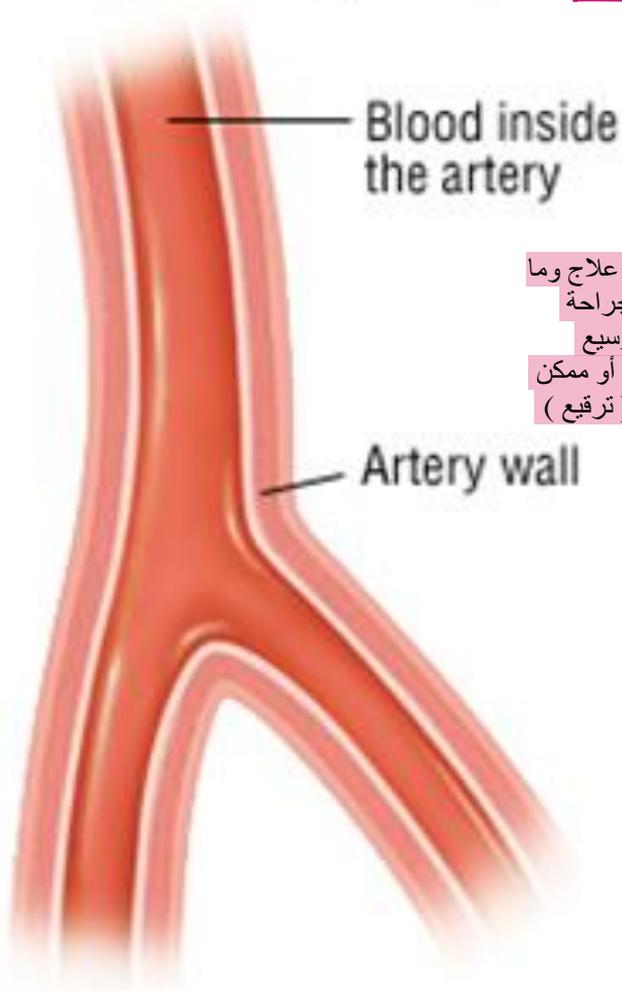
Treatment strategy is based on decreasing the heart demand and improving blood supply to the heart

2

الفكرة بالأدوية هو إنه نقل الجهد على القلب
ونحسن وصول الدم إليه



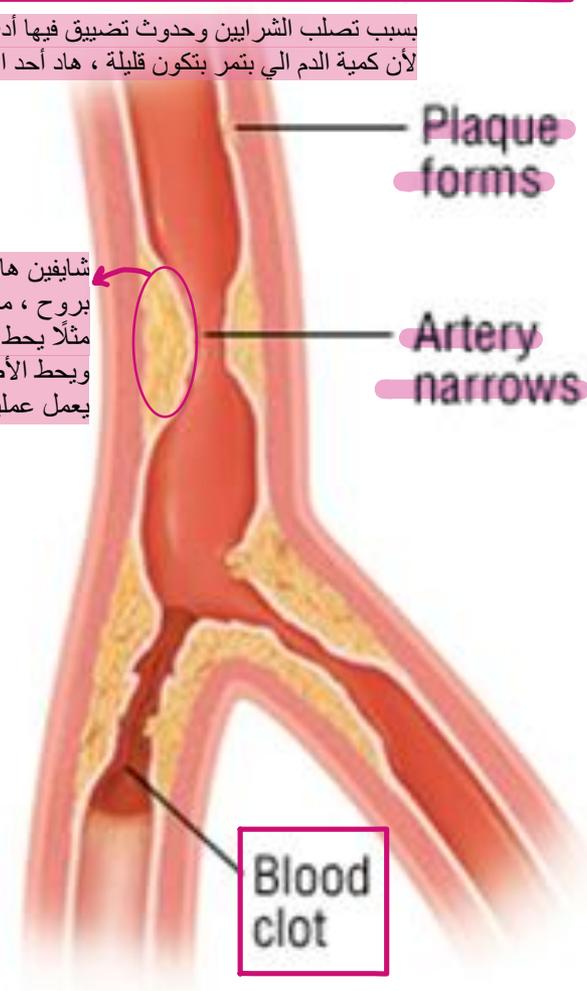
Healthy coronary artery



Atherosclerotic coronary artery

بسبب تصلب الشرايين وحدوث تضيق فيها أدى ذلك لأن كمية الدم الي بتمر بتكون قليلة ، هاد أحد الاسباب

شايقين هاد الأصفر ما إله علاج وما بروح ، ممكن يعمل له جراحة مثلاً يحط شبكية ليعمل توسيع ويحط الأصفر على جنب أو ممكن يعمل عملية قلب مفتوح (ترقيع)



TYPES OF ANGINA

التصنيف بناء على مین قديه تضيق

1. Effort-induced angina, classic or **stable** angina

تضيق قليل، فبحس بالألم والأعراض **عند بذل جهد فقط**، ولو بتتذكروا بالباثو حكينا إنه بخلوا المريض يمشي على treadmill جهاز مشي ولو تعب

2. Prinzmetal, variant, **vasospastic** angina

هون التضيق سببه smooth muscle spasm
فالسبب هون تشنج بالعضلات تبعت الاوعية الدموية بينما بال-
stable and unstable كان جت بسبب الترسبات والتصلب

3. **Unstable** angina or **acute coronary** syndrome

تضيق كثير والألم موجود سواء بذل جهد أو وهو مرتاح

From a spasm of the vascular smooth muscle vasospastic or variant angina

when episodes of angina occur at rest and when there is an increase in the severity, frequency, and duration of chest pain in patients with previously stable angina

لما بحس بالاعراض حط حبة تحت اللسان واموره تمام بتصير

- 1 • In **effort** angina, oxygen demand can be reduced by decreasing cardiac work.
- 2 • In **variant** angina, on the other hand, spasm of coronary vessels can be **reversed** by nitrate or calcium channel-blocking vasodilators.
- 3 • In **unstable** angina, vigorous measures are taken to achieve both—increase oxygen delivery and decrease oxygen demand.

حبة تحت اللسان

تدابير

Statins are very important in effort angina long term treatment

Unstable angina management

تقييم الخطورة

- Risk assessment:

- High risk patient (revascularisation)

لازم اعمل عملية
(شبكة أو قلب مفتوح)

- Low risk (non-invasive management)

تدخل غير جراحي (بالأدوية و lifestyle)،
لكن للأسف الأدوية مش علاج فقط بياخده
عشان حالته ما تصير أسوء وأحافظ على
المرض بنفس الـ level

- Aspirin and clopidogrel together

- Glycoprotein IIb/IIIa inhibitors (Eptifibatide)

- Parntal anticoagulants (low-molecular weight heparin, Fondaprinex)

Percutaneous coronary intervention (angioplasty) : insert catheter from femoral artery. Inject dye to determine the blockage and vessel diameter. Balloon to open the occlusion. Stent.

coronary artery bypass graft

Antianginal

Vasodilator
عشان ازيد التروية

ادوية تقال الـ contraction
عشان اقلل الجهد على القلب

I. **NITRATES** الأكثر استخدامًا

II. **β -ADRENERGIC BLOCKERS**

III. **CALCIUM-CHANNEL BLOCKERS**

IV. **SODIUM-CHANNEL BLOCKER** عشان يقلل الـ depolarization

The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.

Nitric oxide is gas.

للسلبيد
البي تحت

بتقلل ال preload and afterload
بناءً على ال mechanism of action

NITRATES

Unstable orally = first pass metabolism ↑
لهيك بعطوها sublingual تحت اللسان

- **Isosorbide dinitrate** and **isosorbide mononitrate** are solids at room temperature, **nitroglycerin** is only moderately volatile, and **amyl nitrite** is extremely volatile.

أقل شي استخدامًا

- Cause a rapid reduction in myocardial oxygen demand and symptom relief (life saving)
- Nitrates inhibit coronary vasoconstriction or spasm, increasing perfusion of the myocardium and, thus, relieving vasospastic angina.

زدت كمية الدم الواصل للقلب

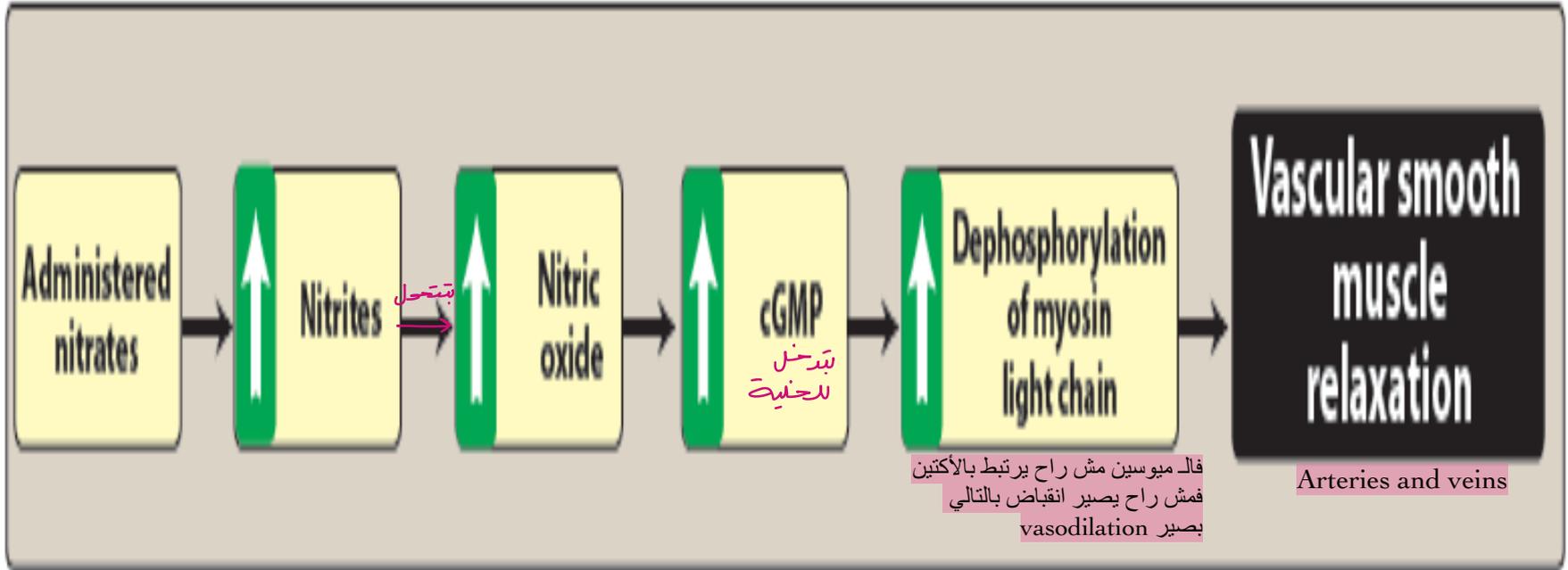
- In addition, nitrates relax the veins (venodilation), decreasing preload and myocardial oxygen consumption

قللت كمية الاكسجين الي يستهلكها القلب عشان يعمل توازن بين القادم والمستهلك

بالوضع الطبيعي عملية رجوع الدم للقلب ما بتعمل عبء وزيادة حمل عليه والقلب بكون كافي ليوسع كمية الدم الطبيعية

بينما لما بكون عندي مشكلة بعضلات الاوعية راح يزيد عندي ال preload (زيادة في كمية الدم الموجودة بالبطين) بوصل القلب دم اكثر "مش عشان يغذي لقلب عشان يعبي البطين"، بالاضافة انه تصبب الشرايين راح يؤدي لزيادة ال after load (المقاومة الي لازم اتغلب عليها لأطلع الدم من القلب)

MOA of Nitrates



Nitrates Improve blood supply and reduce Oxygen demand

+ preload and afterload ↓

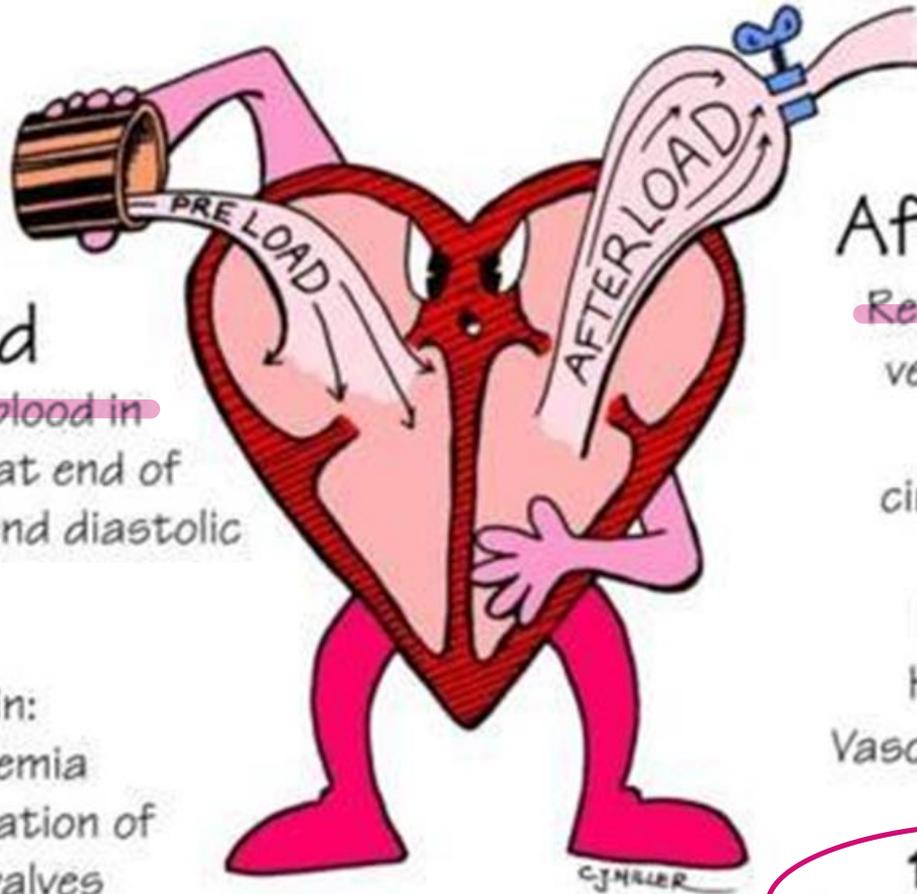
PRELOAD AND AFTERLOAD

Preload

Volume of blood in ventricles at end of diastole (end diastolic pressure)

Increased in:

Hypervolemia
Regurgitation of cardiac valves
Heart Failure



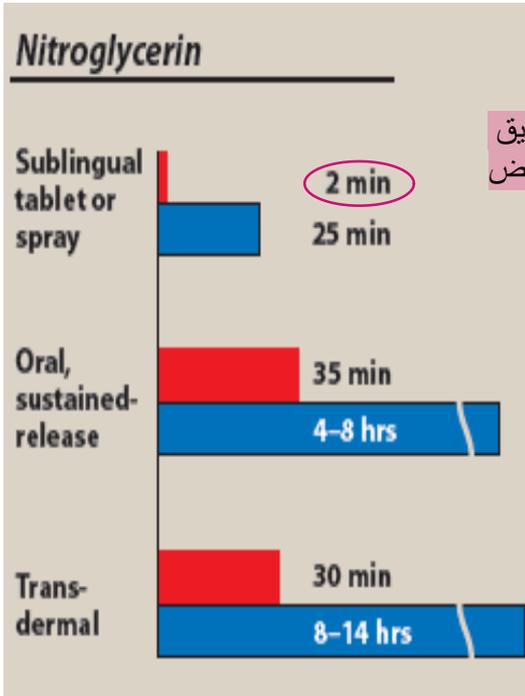
Afterload

Resistance left ventricle must overcome to circulate blood

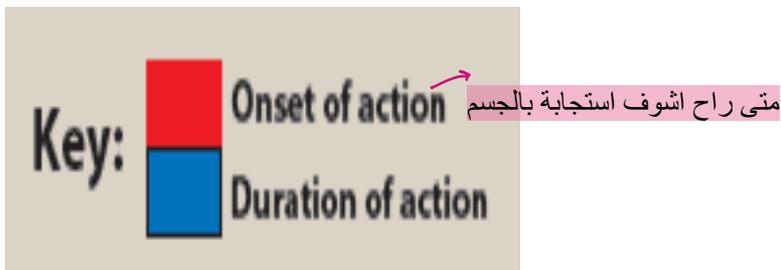
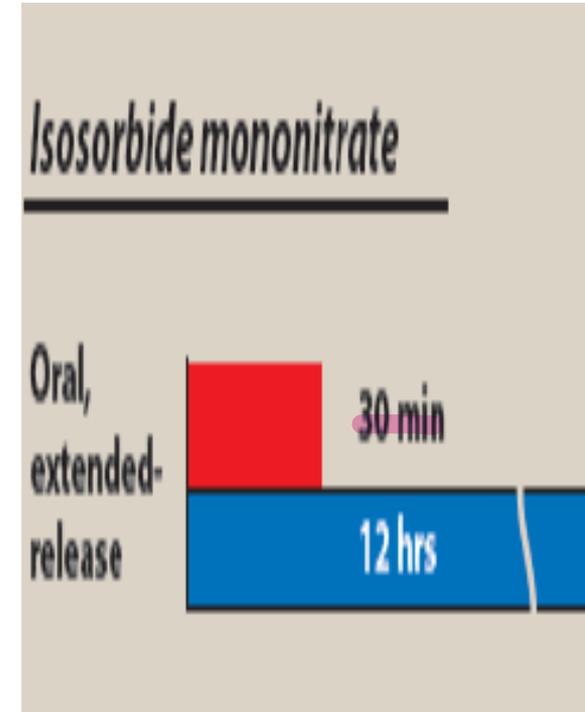
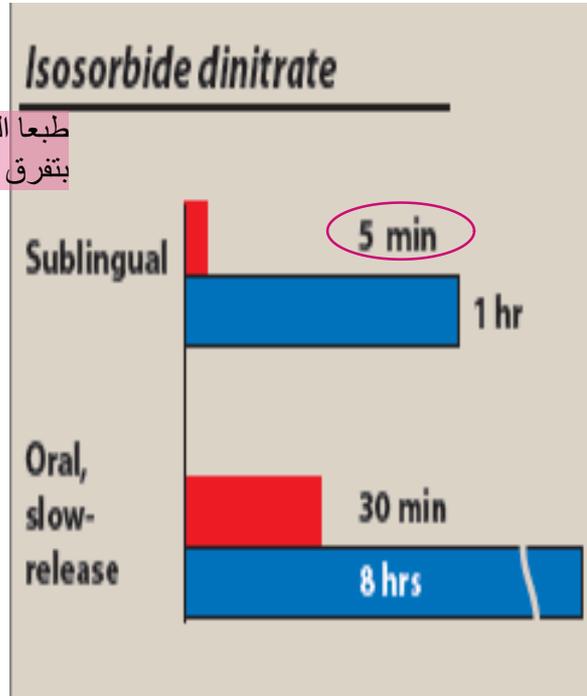
Increased in:
Hypertension
Vasoconstriction

↑ Afterload =
↑ Cardiac workload

Differ in their Kinetics



طبعاً الثلاث دقائق بتفرق مع المريض



Nitroglycerin is the prototype nitrates.

Traditional oral tablets bioavailability is <10-20%

Adverse effects

NOTE :

اي دوا بعمل vasodilation فغالبا بعمل

1. Headache.
2. Nausea and vomiting.
3. Flushing

ومن الممكن أيضاً

Reflex tachycardia and postural hypotension

- Headache is the most frequent*
 - Postural hypotension at high doses
 - Reflex tachycardia
 - C/I with sildenafil ^{فياجرا لأنه بعمل vasodilation}
- Tolerance occur to nitrates, so “nitrates free periods” are important

الدكتور مخربط حاط سلايد بالنوت هههه

Continuous exposure to high levels of nitrates can occur in the chemical industry, especially where explosives are manufactured. When contamination of the workplace with volatile organic nitrate compounds is severe, workers find that upon starting their workweek (Monday), they suffer headache and transient dizziness (“Monday disease”). After a day or so, these symptoms disappear owing to the development of tolerance. Over the weekend, when exposure to the chemicals is reduced, tolerance disappears, so symptoms recur each Monday.

Nitrates free period is between 10-12 hrs

النيترات الها استخدام تاني مثل المتفجرات وهي الي تم استخدامها بتفجير مرفأ بيروت

TABLE 12-3 Nitrate and nitrite drugs used in the treatment of angina.

Drug	Dose	Duration of Action
Short-acting		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
Long-acting		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1–1.5 inches per 4 hours	3–6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours

β -ADRENERGIC BLOCKERS

- The β -adrenergic–blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart

يعمل inhibition of beta 1 & beta 2 والتدفق انها تساعدني بتقليل الجهد على عضلة القلب لفترة مؤقتة ع بين ما نأخذ الإجراء المناسب لطبيعة الحالة

- Due to their ^{β_1} cardioselectivity, *metoprolol* and *atenolol*, are preferred

NOTE that all Beta Blockers lose their selectivity at high doses

With β -blockers, the demand for oxygen by the myocardium is reduced both during exertion and at rest. Because of these effects, β -blockers are the drugs of choice to treat effort-induced angina. The β -blockers reduce the frequency and severity of angina attacks. β -Blockers are ineffective against and should not be used in vasospastic angina

Beta blockers should not be stopped abruptly, but gradually over 2-3 weeks

CALCIUM-CHANNEL BLOCKERS

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that (hypoxia produces)
- 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.

وَيَقْتَلِ الانقباضات فيبتقل كمية الاكسجين المستهلكة

➤ Verapamil	→	Myocardium	Heart rate ↓ contraction ↓
➤ Nifedipine	→	Peripheral	Vasodilation
➤ Diltiazem	→	Intermediate	Both

Use of these agents has thus emerged as the most effective prophylactic treatment for this form of angina pectoris.

Nifedipine

كونه تأثيره على الأوعية الدموية فينبغ
أعطيه مع beta blocker

- ✓ Dihydropyridine derivative
 - ✓ An arteriolar vasodilator
 - ✓ ER oral tablets
 - ✓ Potent vasodilator, beneficial in angina
 - ✓ Cause: headache, flushing, peripheral edema
 - ✓ Reflex tachycardia
- “Avoided in coronary artery disease because of evidence of an increase in mortality after an MI and an increase in acute MI in hypertensive patients”.

In patients with unstable angina, immediate-release nifedipine. are contraindicated because it can increase the risk of adverse cardiac events.

Verapamil

- Diphenylalkylamine
- Slows cardiac atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- **Verapamil** causes greater negative inotropic effects than *nifedipine*, but it is a weaker vasodilator.

بمثال
الانقباضات

Verapamil

- **Contraindicated** in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- Causes constipation
- *Verapamil* increases *digoxin* levels. → So it will be C/I
 - ! Digoxin
 - ! β -blocker

Diltiazem: Dual Mechanism

مع ناس عندهم
angina and HTN

- Similar to verapamil effects but less effective in decreasing HR
- But also it decreases BP
- Useful in HTN with mild angina
- Extensive metabolism

Angina with:

CONCOMITANT DISEASE

DRUGS COMMONLY USED IN TREATING ANGINA



NONE	Long-acting <u>nitrate</u>	<u>β-Blockers</u>	^{CCB} <u>Ca²⁺ channel blockers</u>
RECENT MYOCARDIAL INFARCTION <i>MI</i>	Long-acting <u>nitrate</u>	<u>β-Blockers</u>	
ASTHMA, <u>COPD</u>	Long-acting <u>nitrate</u>		<u>Ca²⁺ channel blockers</u>
HYPERTENSION	Long-acting nitrate	<u>β-Blockers</u>	<u>Ca²⁺ channel blockers</u>
DIABETES	Long-acting <u>nitrate</u>		<u>Ca²⁺ channel blockers</u>
CHRONIC RENAL DISEASE	Long-acting <u>nitrate</u>	β-Blockers	<u>Ca²⁺ channel blockers</u>

KEY:

Drug class
Commonly used drugs

Drug class
Less effective drugs

SODIUM-CHANNEL BLOCKER

Ranolazine

بمنع يصير عندي depolarization فبمنع يتكون الـ action potential فبالتالي مش راح يصير عنا انقباضات بسبب انه اصلا كمان ما راح يسمح بتبادل الـ Na-Ca

- **Ranolazine** is a new antianginal drug that acts by reducing sodium current that facilitates calcium entry via the sodium-calcium exchanger.
- The resulting reduction in intracellular calcium concentration reduces cardiac contractility and work.

sodium-calcium exchanger enters sodium exit calcium

ممكن اعمل combination

