# DRUGS USED IN DISORDERS OF THE CARDIOVASCULAR SYSTEM

Lecture 3:

**Coronary Heart Disease, Angina Pectoris and Anti-Anginal Agents**

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Photo: Photograph of chordae tendineae attached to papillary muscles of a ventricle, Seeley's anatomy & physiology, 10th ed. New York, NY, McGraw-Hill 2010

# Learning Objectives:

1. The pathophysiological basis for the development of angina pectoris and other ischemic coronary syndromes
2. The indications, mechanisms of action, adverse effects and contraindications of drugs commonly used in the treatment of angina
3. How pharmacological therapies are used along with non-pharmacological approaches to the relief of angina and other ischemic coronary syndromes

**Pharmacology of Nitric Oxide**

4. The physiologic processes that can generate endogenous nitric oxide
5. The isoforms of the enzymes responsible for synthesis of nitric oxide
6. The drugs that can increase levels of endogenous nitric oxide
7. The therapeutic uses of nitrates

Companion eNotes: Cardiovascular Pharmacology
Textbook: Katzung BG Ch. 12 Vasodilators & the Treatment of Angina Pectoris. Pgs. 193-209. In: *Katzung BG, ed. Basic & Clinical Pharmacology*. 12th ed.

# Classification Schema: ANTI-ANGINALS with Relevant Drugs

**Organic Nitrates**
Nitroglycerin [Glyceryl trinitrate (GTN)]
Isosorbide dinitrate
Isosorbide mononitrate

**Calcium Channel Blockers**
Nifedipine
Nicardipine
Amlodipine
Verapamil
Diltiazem

**Beta Receptor Antagonists**
Propranolol
Nadolol
Atenolol
Metoprolol
Carvedilol

**pFOX Inhibitor**
Ranolazine

N.B. Organic Nitrites (e.g., amyl nitrite, isobutyl nitrite), contain the nitrite functional group, cause release of nitric oxide such as the MOA of the organic nitrates, but are not used to treat angina.

# Diagnostic Classifications & Terminology

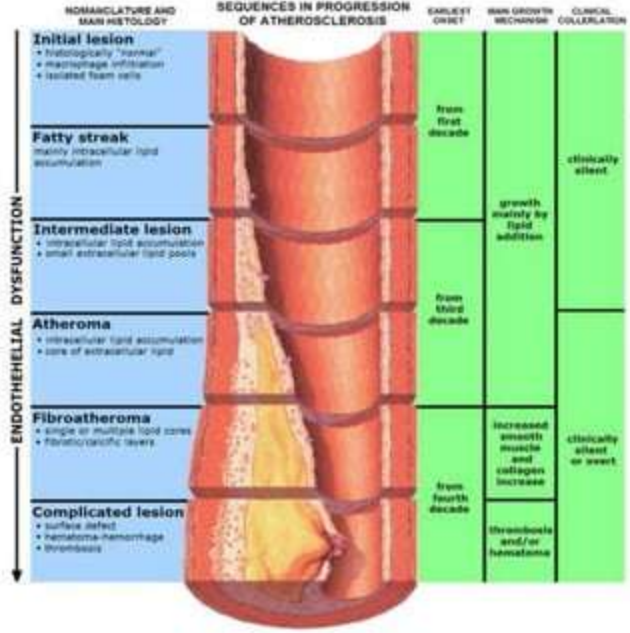
- Anatomic (Pathologic) Diagnosis= Atherosclerosis (ASHD)
- Etiologic Diagnosis= Coronary Heart Disease (CHD, IHD, CAD)
- Physiologic Diagnosis= Angina Pectoris
- Functional Diagnosis= Stable vs Unstable Angina vs ACS

# Coronary heart disease (CHD) Defined (Etiologic Dx)

- **Coronary heart disease** (CHD) is a condition in which proper circulation of blood and oxygen are not provided to heart and surrounding tissue
- Result is due to a narrowing of small blood vessels, which normally supply heart with blood and oxygen
- **Coronary heart disease**, a type of cardiovascular disease, is the leading cause of death for both men and women in the United States

# Causes (Anatomic Dx)

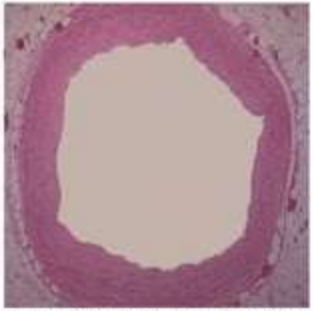
- The typical **cause of coronary heart disease** is **atherosclerosis**, which takes place with plaque and fatty build up on the artery walls, narrowing the vessels



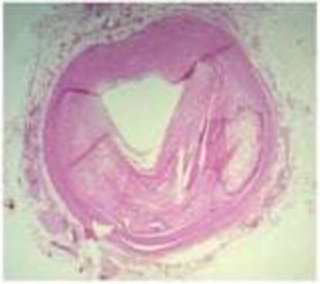
# Arteriosclerosis

- **Arteriosclerosis** is a general term for several disorders that cause **thickening** and **loss of elasticity** in the **arterial wall**
  - **Atherosclerosis**, the most common form, is also the most serious because it **causes coronary artery disease** and **cerebrovascular disease**

- **Atherosclerosis** is patchy intimal plaques **(atheromas)** in medium-sized and large arteries
  - The plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue



Normal coronary artery, microscopic



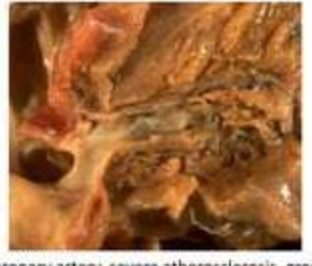
Coronary artery with atherosclerotic narrowing, microscopic

From: Webpath Cardiovascular Pathology Image plates

# Pathobiology of Atherosclerosis

- When excess cholesterol deposits on cells and on the inside walls of blood vessels it **forms an atherosclerotic plaque**
- The **first step** of atherosclerosis is **injury to the endothelium** which results in atherosclerotic lesion formation
- When the **plaque ruptures**, **blood clots form** which lead to decreased blood flow, resulting in **cardiovascular events** **(ACS)**

Coronary artery, mild atherosclerosis, gross

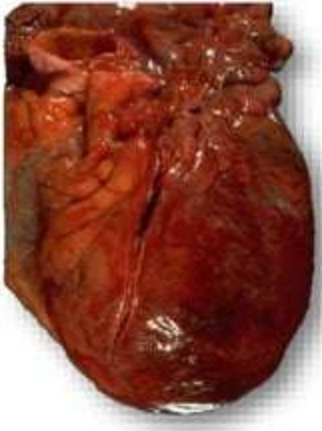


Coronary artery, severe atherosclerosis, gross

From: Webpath Cardiovascular Pathology image plates

# Pathobiology of Atherosclerosis (2)

- **Symptoms** develop when growth or rupture of the plaque reduces or obstructs blood flow
- **Diagnosis** is clinical and confirmed by angiography, ultrasonography, or other imaging tests
- **Treatment** includes risk factor and dietary , modification, physical activity, antiplatelet drugs, and antiatherogenic drugs



**Heart and LAD coronary artery with recent thrombus, gross**

- The anterior surface of the heart demonstrates an opened left anterior descending coronary artery.
- Within the lumen of the coronary can be seen a dark red recent coronary thrombosis.
- The dull red color to the myocardium as seen below the glistening epicardium to the lower right of the thrombus is consistent with underlying myocardial infarction

*From: Webpath Cardiovascular Pathology image plates*

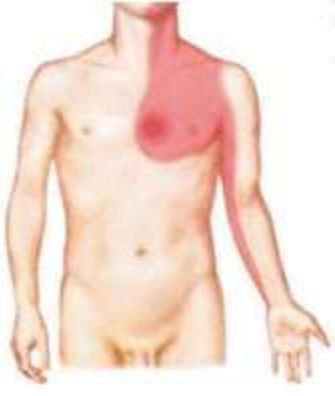
# Risk Factors for Atherosclerosis

**Risk factors atherosclerosis include:**

- **Dyslipidemia (hypercholesterolemia/LDL-C)**
- diabetes
- **cigarette smoking**
- family history
- sedentary lifestyle
- obesity
- **hypertension**

# Angina Pectoris Overview

**Angina,** or angina pectoris (AP), **is a gripping** (vice-like or pressure-like) pain felt in the center of the chest that **may radiate to the neck, jaw, and arms** and is caused most often by exercise; emotion, eating, and cold weather are other causes



Characteristic distribution of pain in angina pectoris

# AP Overview (2), The 3 types of Angina:

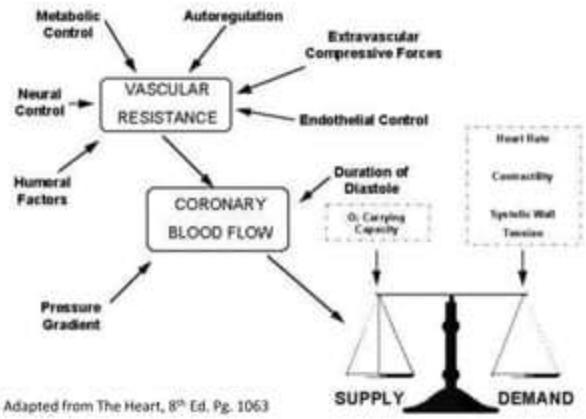
- **Stable angina** (**exertional or typical angina**), caused by atherosclerosis
  - treatment is intended to reduce cardiac load and increase myocardial blood flow
- **Vasospastic angina** (variant or Prinzmetal angina), caused by severe coronary vessel contraction (vasospasm), with **chest pain at rest**
  - drugs aimed to stop vasospasm
- **Unstable angina** (crescendo angina), in which **pain occurs without stress** (or at rest or w increase frequency or not relieved with rest & SL-NTG as in stable angina) *(part of the ACS complex)*
  - Nitrates and β blockers are used, as are calcium channel antagonists if mechanism is vasospasm
  - Reducing platelet function and thrombotic episodes helps decrease mortality in unstable angina

# Common precipitating factors in angina pectoris

- Exertion
- Stress
- Exercise
- Heavy meal
- Cold
- Smoking

# Pathophysiology of Angina Pectoris
## Coronary Artery $O_2$ Supply and Demand

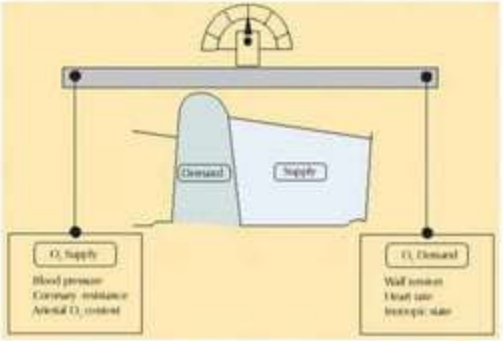
AP occurs when the heart receives deficient oxygen because of blood vessel narrowing, which results mainly from aging and also from cigarette smoking, high cholesterol levels, obesity, and diabetes




Adapted from The Heart, 8th Ed. Pg. 1063

# Pathophysiology of AP (Chest Pain) (2)

- When the supply of oxygen and nutrients in the blood is insufficient to meet the demands of the heart, the heart muscle **aches**
- The heart demands a large supply of oxygen to meet the demands placed on it




The myocardial supply: demand ratio--a critical review.
[Am J Cardiol. 1978]

# CAD Risk Factors

**Certain conditions are considered to put an individual at greater risk for coronary heart disease**

The following are some risk factors: (same as for atherosclerosis in general)

1. Age (particularly 40+)
2. Diabetes
3. Genetics (heredity)
4. **High blood pressure**
5. **High bad cholesterol (LDL)**
6. Increased levels of C-reactive protein, fibrinogen, or homocysteine
7. Lack of sufficient physical activity
8. Low good cholesterol (HDL)
9. Menopause
10. Obesity
11. **Smoking**

# Symptoms OF CHD

**Some more frequent symptoms of coronary heart disease include:**

1. Angina (ischemic pain)
2. Myocardial Infarction
3. Shortness of breath

# Diagnosis

**Diagnosis of CHD may be accomplished by a variety of means:**

1. Coronary angiography
2. Coronary arteriography
3. Coronary CT angiography
4. Echocardiogram
5. Electrocardiogram (ECG)
6. Electron-beam CT (EBCT)
7. Exercise stress test
8. Magnetic resonance angiography
9. Nuclear scan

# Treatment

Coronary heart disease treatment methods may include:
(depends on the presenting Physiologic Dx)

1. **Angioplasty with stenting**
2. Coronary artery bypass surgery (CABG)
3. **Medication**
4. Minimally invasive heart surgery
5. Proper diet and exercise
6. Quitting smoking
7. Treatment of other comorbidities, HTN, DM, Obesity

# Antianginal Pharmacologic Agents

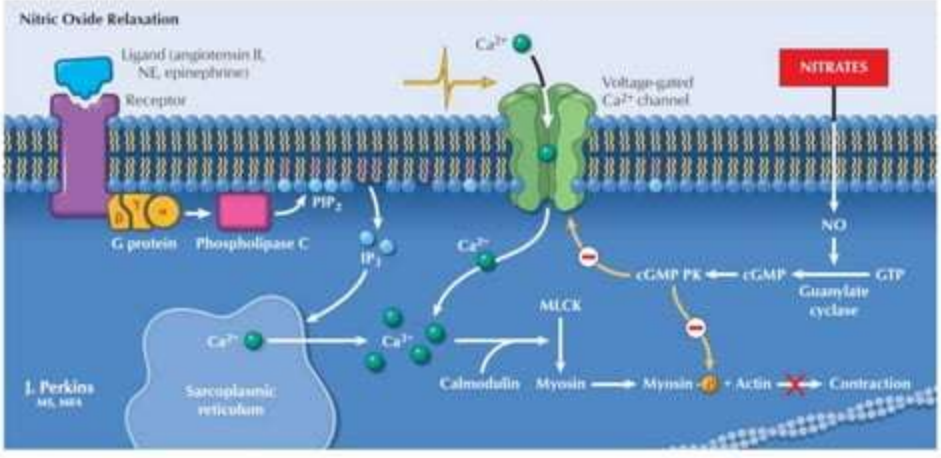
- Nitrates
- Beta blockers
- Calcium channel blockers

**Before covering the nitrates let us first talk about nitric oxide, since nitrates are agents that work by causing the release nitric oxide.**

Also remember, the organic nitrites (e.g., amyl nitrite, isobutyl nitrite), contain the nitrite functional group, and cause release of nitric oxide such as the MOA of the organic nitrates, but are not used to treat angina

# Nitric oxide

**Nitrates are agents that release nitric oxide (NO)**




**NO binds to guanylyl cyclase**, leading to an increase in **cGMP** and protein kinase G (PKG)>>> **vasodilation**

# Nitric oxide* (2)

**Nitric oxide (*INOmax*)** is a gaseous signaling molecule that dilates blood vessels and protects them against thrombosis and atherogenesis

There are three **nitric oxide synthase enzymes** that **produce NO**:

1. nNOS (neural)
2. eNOS (endothelial)
3. iNOS (inducible)
   i. **nNOS and eNOS** are constitutively active and **regulated by calcium**
   ii. **iNOS** is activated in macrophages in response to inflammatory mediators>>>it is **not regulated by calcium**

* Note: nitric oxide (NO), the vasodilator, should not be confused with nitrous oxide (N2O), the anesthetic.

# Nitric oxide (3)

- NO binds to guanylyl cyclase>>> leading to an increase in cGMP and protein kinase G (PKG)
  - This pathway leads to vasodilation

- NO can also be toxic to cells
  - The antioxidant glutathione protects cells from the oxidative effects of NO

- Currently, it is believed that selective iNOS inhibition would permit the positive effects of NO while preventing the negative effects
  - However, there is no iNOS-specific inhibitor on the market at this time

# Strategies for Treating Cardiovascular Diseases: Angina

## Therapeutic Goal

**Reduce work** of the heart and **improve** cardiac **circulation** =
**Decrease** myocardial O2 **demand**
**Increase** myocardial O2 **supply**

## Pharmacologic Strategies

**Stable Angina**

**Nitroglycerin** reduces preload by venodilation

**Atenolol** decreases myocardial work (β1 antagonists)

**Diltiazem** decreases BP through vasodilation by blocking calcium entry

**Unstable Angina**

**β-Blockers** reduce rate and myocardial work

**Aspirin** prevents platelet aggregation in myocardial arteries

**Heparin** inhibits clotting in myocardial arteries

**Nitroglycerin** reduces preload

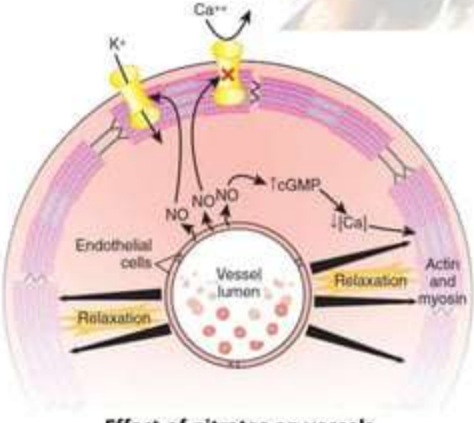
**Eptifibatide** or **Tirofiban** inhibit platelet aggregation

# Antianginal Pharmacologic Agents: Nitrates

❑ **Prototype:** nitroglycerin (NTG)
Others drugs: isosorbide dinitrate (ISDN), isosorbide-5-mononitrate

❑ **MOA (Mechanism of Action)**
These agents all release NO

- **NO, also known as** endothelium-derived relaxing factor **(EDRF) induces vasodilation primarily on** the **venous side** of the circulation (venodilation)
- It does this by **activating guanylyl cyclase**, an enzyme that **produces cGMP**, which **decreases Ca+** entry into cells and causes **relaxation of vascular smooth muscle**




**Effect of nitrates on vessels**

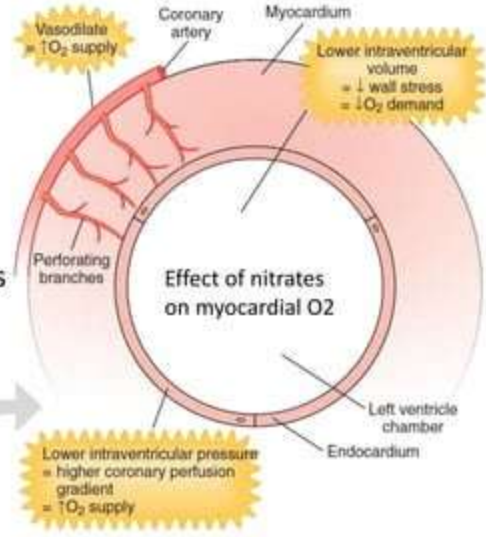
Bardal SK, Waechter JE and Martin DS. Applied pharmacology. 2011

# Antianginal Pharmacologic Agents:
# Nitrates (2)

- **MOA (Mechanism of Action)** cont.
  - The venodilatory effect produces a pooling of blood in the venous capacitance vessels>>> resulting in a **reduction in venous return, preload, and end diastolic pressure**, which:
    - Lowers ventricular wall tension>>>reduces oxygen demand and
    - Improves the coronary pressure gradient
      - Pressure gradient=

    Coronary pressure - End diastolic pressure

**These two mechanisms improve supply-demand balance of the myocardium and are the primary mechanisms by which NTG relieves angina**




Bardal SK, Waechter JE and Martin DS. Applied pharmacology. 2011

# Antianginal Pharmacologic Agents: Nitrates (3)

## ❑ Pharmacokinetics

- Elimination half-time of NTG is 1.5 minutes
- NTG has very low oral bioavailability and therefore is administered topically (patch or ointment), sublingually (pill or spray), or intravenously
- Sublingual preparations have a rapid onset and therefore are useful in relieving acute angina attacks
- ISDN and isosorbide mononitrate have longer half-lives and the advantage of oral administration
- Tolerance can develop to nitrates
  - Particularly true of long-acting agents
    - Patches are therefore usually worn 12 hours on and then 12 hours off

# Antianginal Pharmacologic Agents: Nitrates (4)

❑ **Indications:**

- Stable angina: treatment and prevention
- Acute coronary syndromes (ACSs):
  - Unstable angina
  - Acute MI
- CHF
- Hypertensive emergency
- To decrease uterine muscle tone (a less common use):
  - To treat premature labor
  - To treat fetal distress caused by high uterine contraction

# Antianginal Pharmacologic Agents: Nitrates (5)

## ❑ Contraindications:

- Hypotension
- Coadministration of PDE5 inhibitors (see next slide)
- Elevated intracranial pressure (ICP)—Vasodilation of cerebral arteries increases cerebral blood volume, which further increases ICP

## ❑ Side Effects:

- Headache: A direct result of the cerebral dilation
- Flushing: Caused by cutaneous vasodilation
- Orthostatic hypotension: Low BP upon standing
- Presyncope or syncope: Caused by the hypotensive effect

# Antianginal Pharmacologic Agents: Nitrates (6)

**Important Notes:**

- The **drug interaction with PDE5 inhibitors** (vasodilators used for treatment of erectile dysfunction) **is significant**
- Many men with erectile dysfunction are older and have heart problems, such as angina
- **Both classes of drugs increase intracellular cGMP**, and the **hypotension** that develops from the profound vasodilation can be **severe and refractory to treatment**
- Hence there is great potential for this interaction to occur and for potentially serious consequences if it does occur (Thus, coadministration is contraindicated)

**Potential for cardiac ischemia false positive:**

- NTG can relax any and all smooth muscle
- Esophageal spasm can mimic angina
- NTG will relax the esophagus and trick the clinician into thinking that the patient does indeed have cardiac ischemia when the **"angina equivalent"** is relieved

# THE END

WAKE
UP
AND

THANK YOU FOR
YOUR ATTENTION

**Further study (SDL):**
Online resource center: Medical Pharmacology Cloud Folder

**Recommended Reading:**
Antianginal Drugs
Clinical: eMedicine articles.
- Coronary Artery Disease
- Risk Factors for CAD
- Angina Pectoris

**Lectures/discussions to follow:**
4. Heart Failure
5. Arrhythmias
6. Hypertension
7. Peripheral Vascular Disease