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CARDIOVASCULAR SEQUENCE

Coronary Artery Disease: Chronic Disease

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Fall 2012

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Grants: NIH, Hewlett Foundation,

Mardigian Foundation, Varbedian Fund, GORE

Consultant: NIH NHLBI

CHRONIC CORONARY ARTERY DISEASE

Key Words: Coronary plaque, angina pectoris, myocardial oxygen supply/ demand, diagnostic tests for CAD

Objectives:

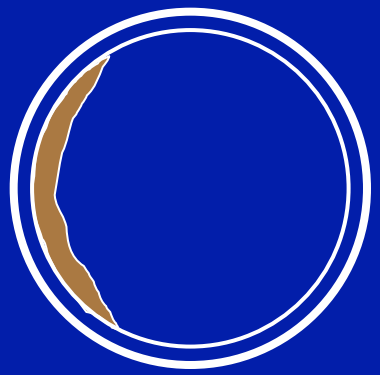
1. To learn how chronic CAD forms.
2. To learn how chronic CAD presents and is identified
3. To learn how chronic CAD is treated.
4. To become familiar with risk stratification in chronic CAD.

OUTLINE

- Development of CAD
- Clinical presentation/definitions
- Concept of myocardial oxygen supply and demand
- Pathophysiology of chronic ischemia syndromes
- Diagnosis
- Treatment strategies
- Prognosis

DEVELOPMENT OF CAD
AHA CLASSIFICATION OF CAD

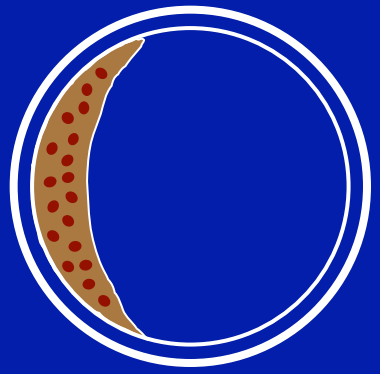
TYPE I



Initial Lesion

- From 1st decade of life
- Clinically silent

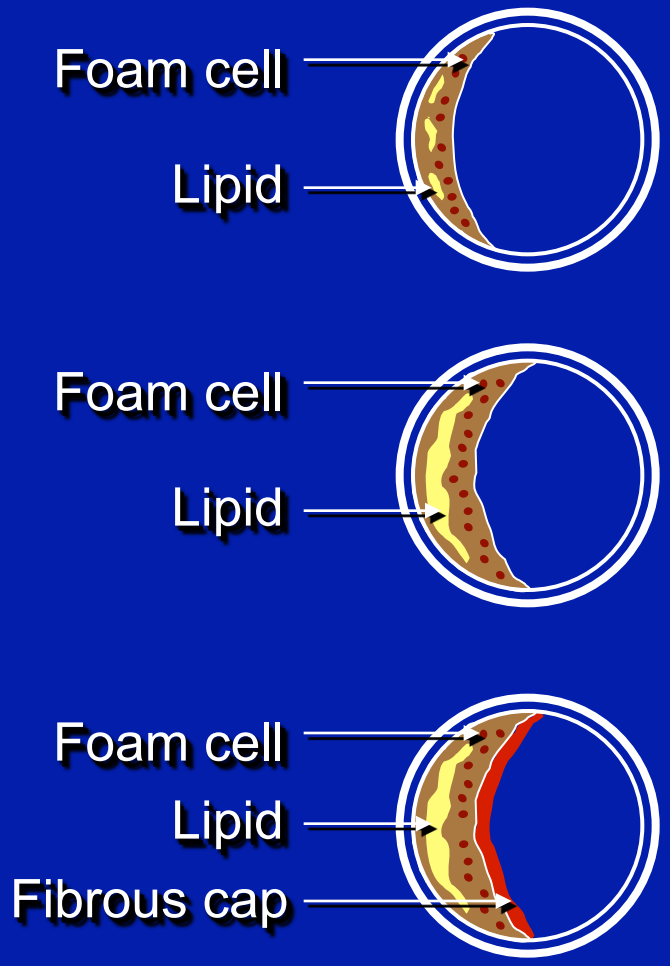
TYPE II



Fatty Streak

- From 1st decade of life
- Growth by lipid accumulation
- Clinically silent

AHA CLASSIFICATION



Intermediate

- From 3rd decade
- Further lipid pool
- Clinically silent

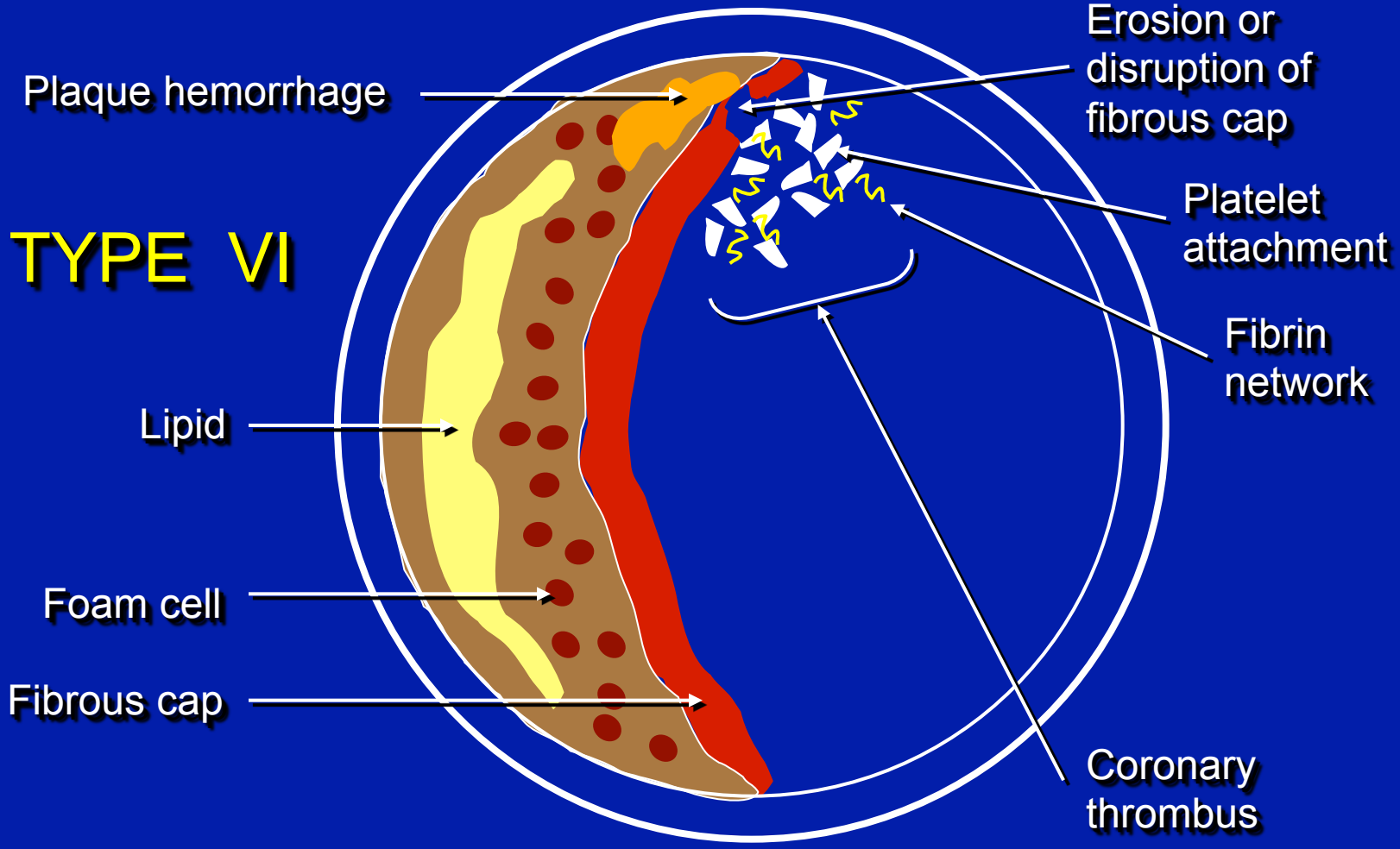
Atheroma

- From 4th decade
- More lipid pool
- Clinically silent or overt

Fibroatheroma

- Lipid core
- Fibrotic layer
- Smooth muscle cells
- Clinically silent or overt

AHA CLASSIFICATION



Complicated Plaque

- Surface defect
- Surface clot
- Hemorrhage in plaque
- Luminal thrombus
- From 4th decade
- Clinically overt

Clinical Presentation / Definitions

A. Definitions

Classic Angina:

Transient discomfort or pain sensation occuring in the precordium, provoked by stress (physical or mental) and relieved by rest or nitroglycerin.

Atypical Angina:

Transient discomfort or pain that is lacking one or more of the criteria of classic angina.

Angina Equivalent:

Sensation of dyspnea, fatigue, or weakness as a manifestation of cardiac ischemia.

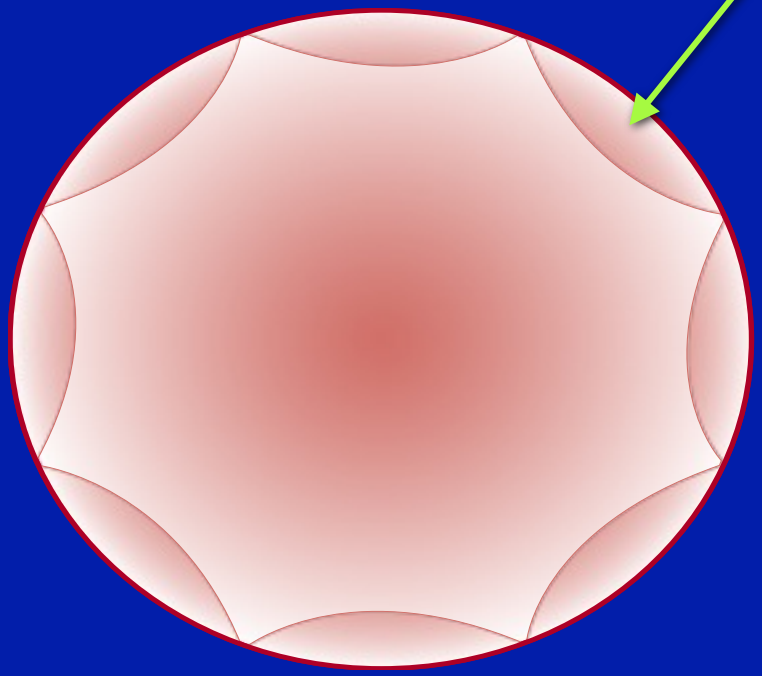
CLINICAL PRESENTATION / DEFINITIONS

B. CHARACTERISTICS

1. Provoked by physical or mental stress
2. Associated with ST-segment depression
3. Lasts ≤ 15 minutes
4. Exercise testing usually provokes chest pain and produces ST-segment depression
5. Medical treatment with beta blockers, nitrates, or calcium channel blockers improves symptoms

Chronic CAD

Normal

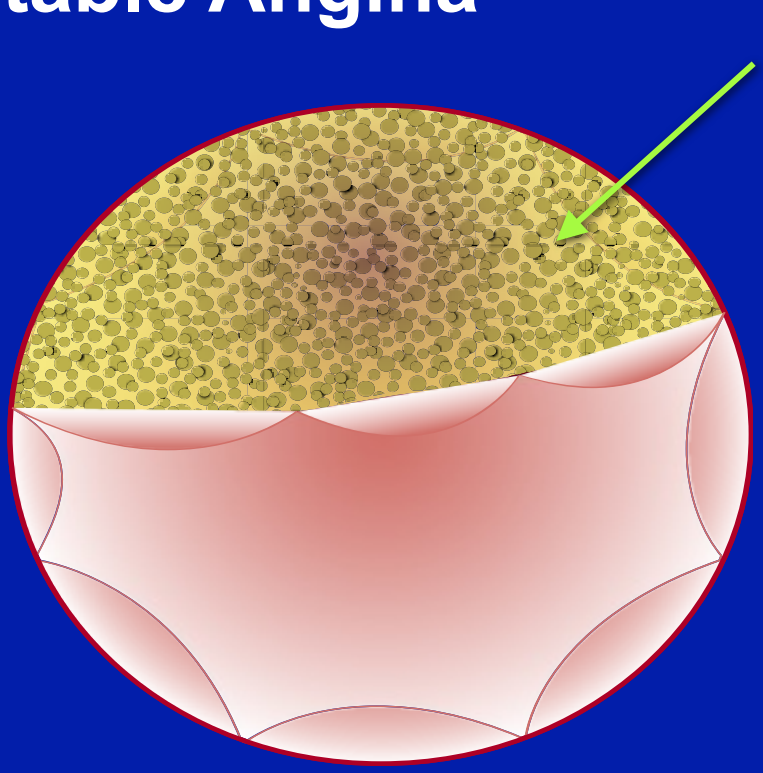


- **Patent lumen**
- **Normal endothelial function**
- **Platelet aggregation inhibited**

 Lilly LS. Pathophysiology of Heart Disease 2007:152.

Chronic CAD

Stable Angina

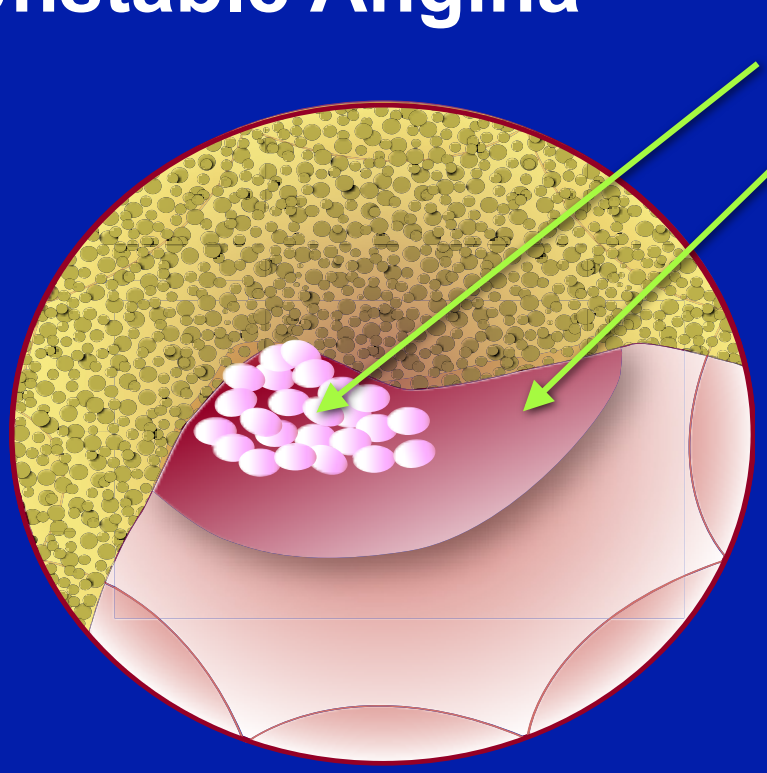


- Lumen narrowed by plaque
- Inappropriate vasoconstriction

Lilly LS. Pathophysiology of Heart Disease 2007; 152.

Chronic CAD

Unstable Angina

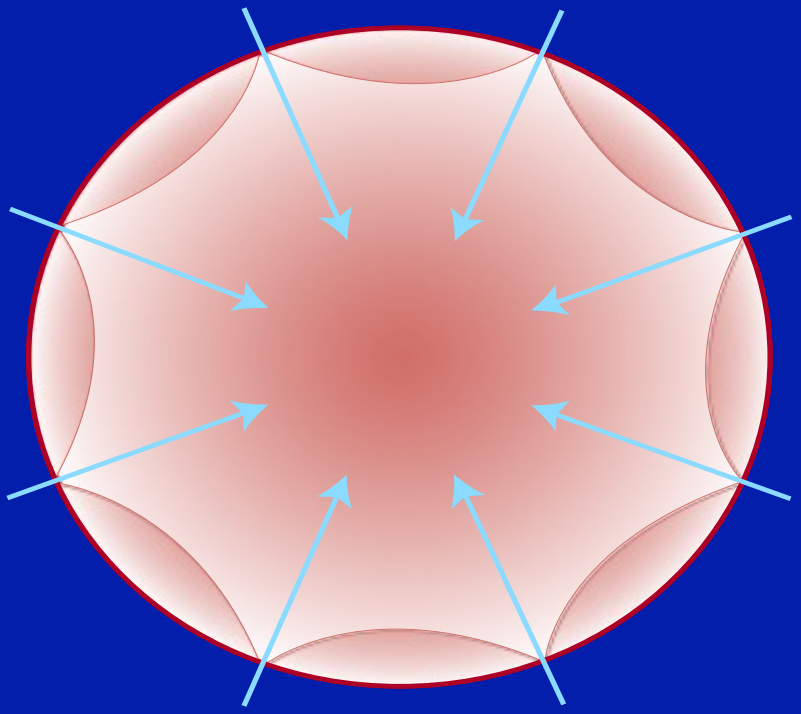


- Plaque rupture
- Platelet aggregation
- Thrombus formation
- Unopposed vasoconstriction

Lilly LS. Pathophysiology of Heart Disease. 2007:152..

Chronic CAD

Variant Angina



- No overt plaques
- Intense vasospasm

Lilly LS. Pathophysiology of Heart Disease. 2007:152.

Grading Of Angina Pectoris By The Canadian Cardiovascular Society Classification System

Class I:

Ordinary physical activity does not cause angina, such as walking, climbing stairs.

Class II:

Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after a meal, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Reference: JACC 1999; 33: 2092-197

Grading Of Angina Pectoris By The Canadian Cardiovascular Society Classification System

Class III:

Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV:

Inability to carry on any physical activity without discomfort-anginal symptoms may be present at rest.

Reference: JACC 1999; 33: 2092-197

PATHOPHYSIOLOGY

DETERMINATES OF MYOCARDIAL OXYGEN SUPPLY AND DEMAND

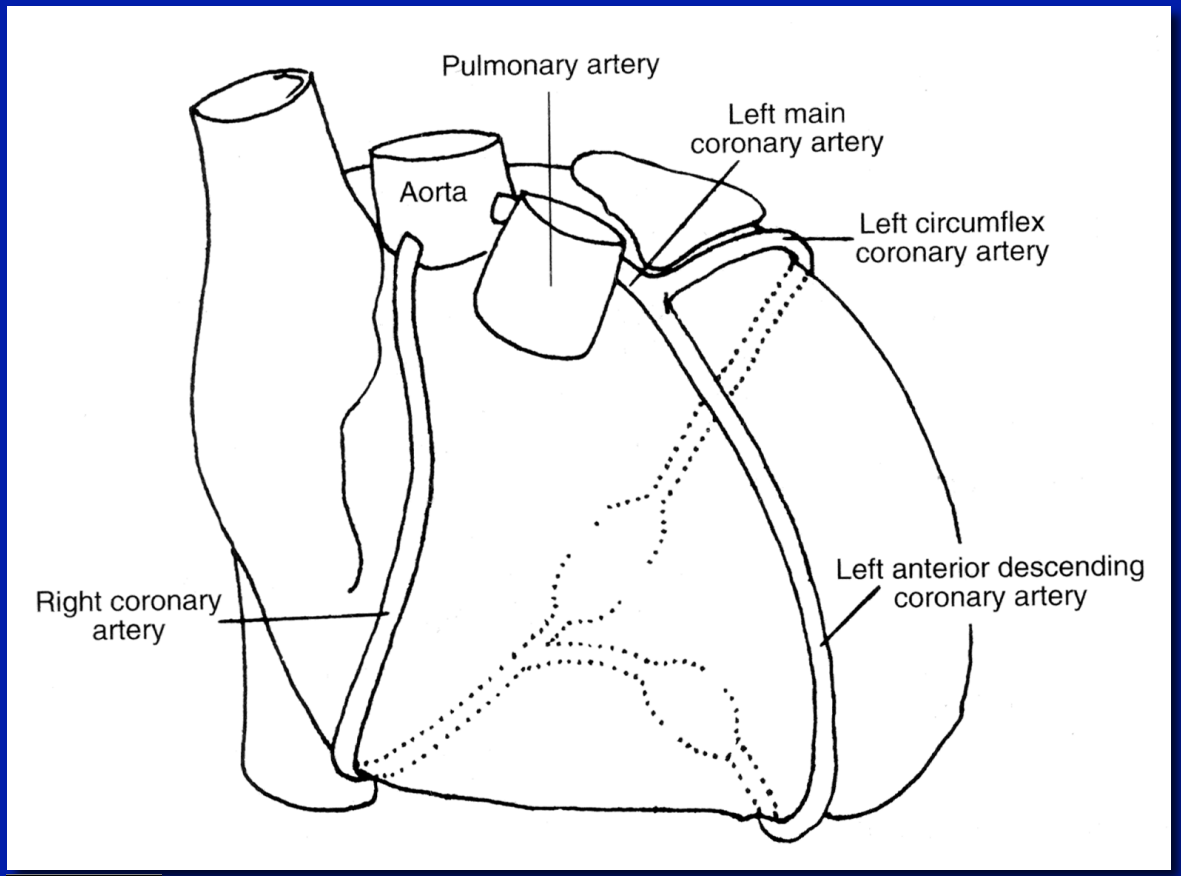
CORONARY BLOOD FLOW

- Vascular tone
- Coronary perfusion pressure
- Collaterals
- Duration of diastole

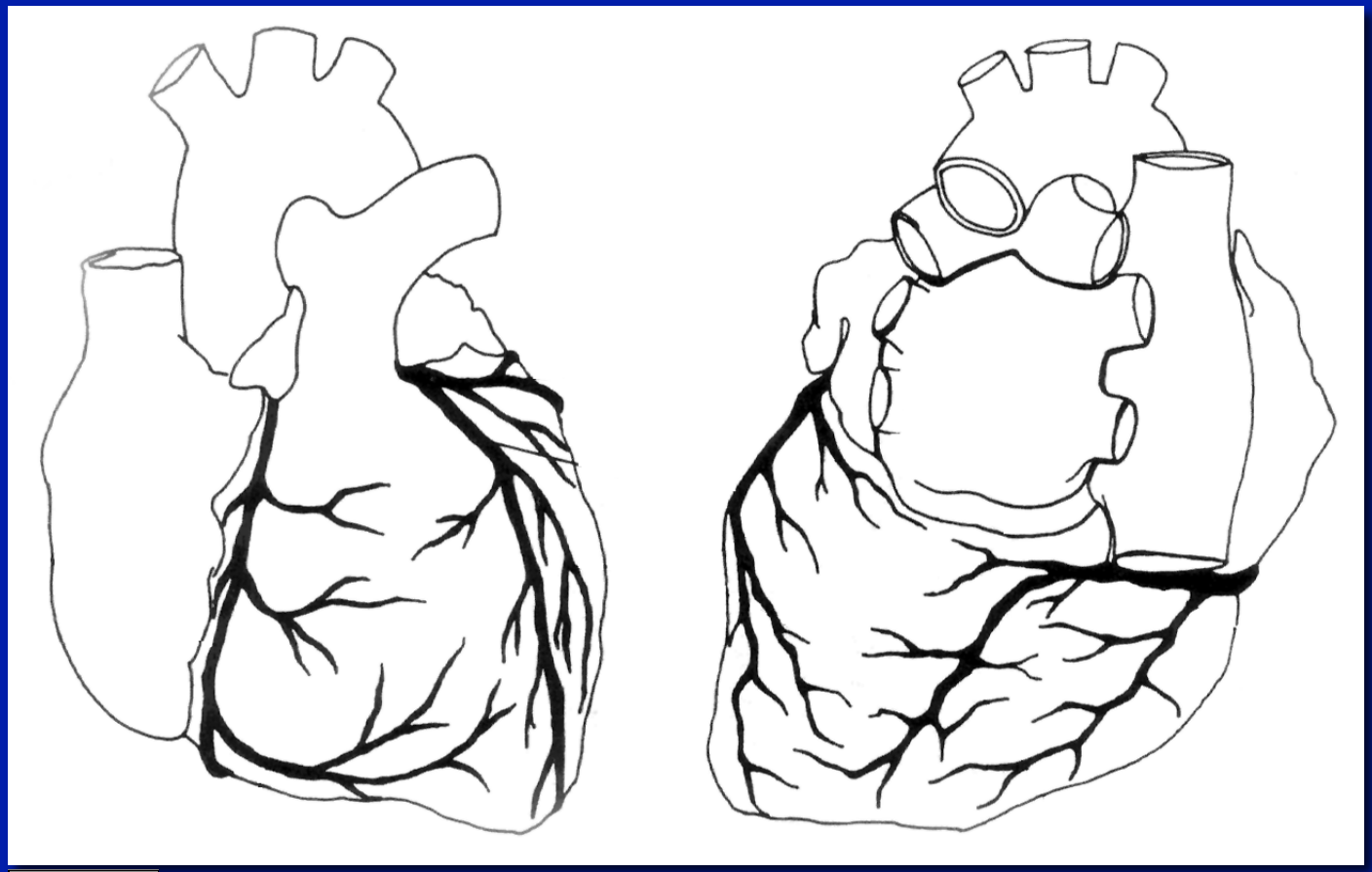
MYOCARDIAL O_2 CONSUMPTION

- Wall tension
- Contractility
- Heart rate
- Preload
- Afterload

COLLATERAL FLOW



COLLATERAL FLOW



VASCULAR TONE

- External arterial compression during systole
- Intrinsic autoregulation
  - Metabolic factors
    - Reduced oxygen → vasodilation
    - Reduced ATP → adenosine → vasodilation
  - Endothelial factors
    - EDRF - NO → vasodilation
    - Prostacyclin → vasodilation
    - Endothelin-1 → vasoconstriction
  - Neural factors
    - α – adrenergic receptors → vasoconstriction
    - β – adrenergic receptors → vasodilation

Coronary Perfusion Pressure

- Approximated by diastolic blood pressure (DBP)
- Marked reductions in DBP lead to hypoperfusion… eg. hypotension, severe aortic valve regurgitation

DIASTOLE

- Flow to coronaries in systole reduced by:
  - external compression of arteries
  - local venturi effect in ascending aorta
- Heart rate ↑ compromises diastolic filling time

Heart Rate

- ↑ # of contractions requires more ATP generation…. this requires more oxygen

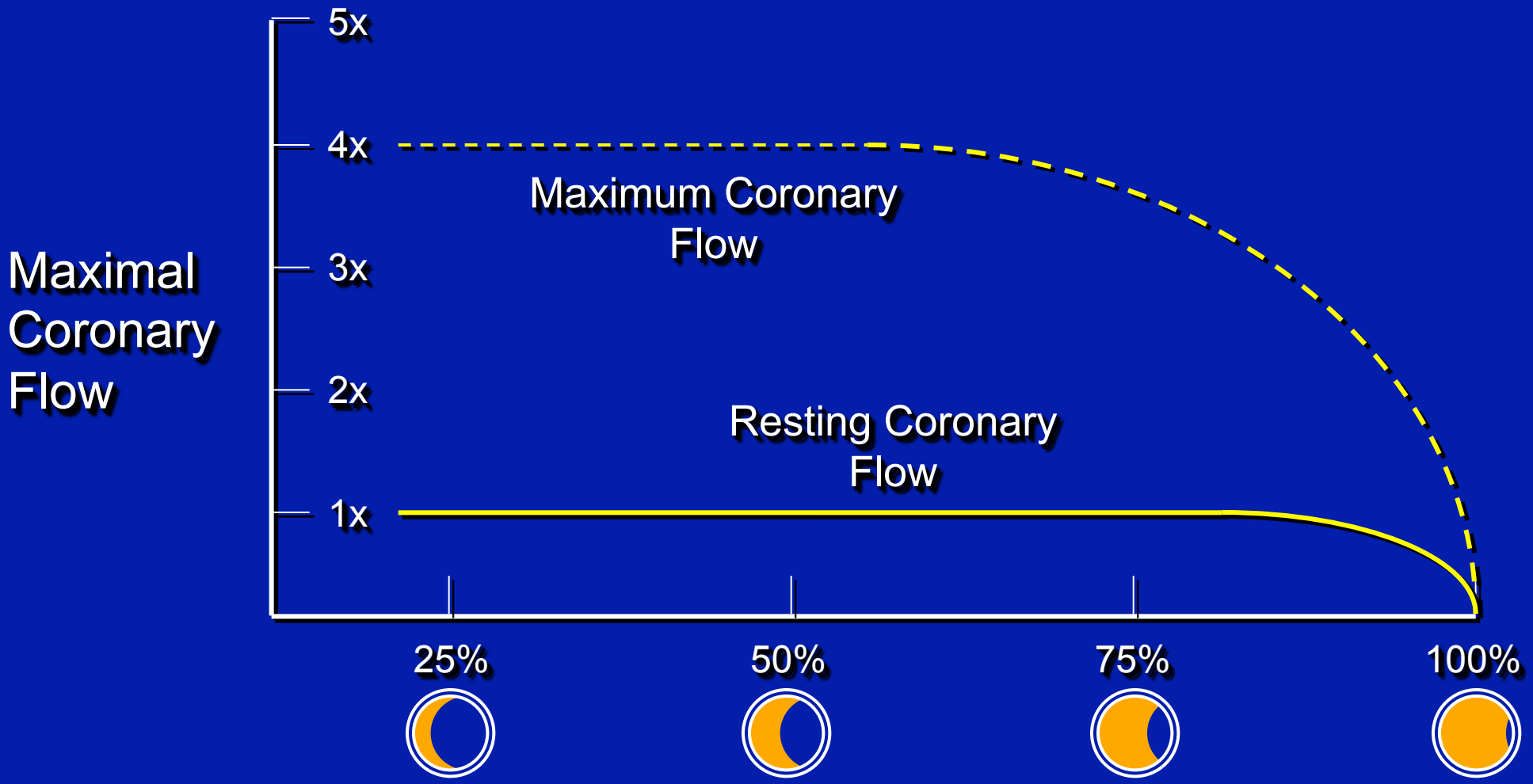
Contractility

- ↑ Force of contraction requires more ATP…. increases O_2 consumption

PATHOPHYSIOLOGY OF CHRONIC ISCHEMIC SYNDROMES

- Fixed vessel narrowing
- Endothelial cell dysfunction
- Non-Coronary factors

FIXED VESSEL STENOSIS



ENDOTHELIAL CELL DYSFUNCTION

- Normal response to stress: vasodilation….increased blood flow/shear stress → sympathetic activation → EDRF - NO
- Normal vessel: EDRF - NO outweighs α - constriction from catecholamines
- Diseased vessel: vasoconstrictive response overcomes inadequate EDRF - NO release…."sensitized" to vasoconstrictive platelet products

NON-CORONARY FACTORS

Inadequate Oxygen Supply

- Anemia
- Hypoxia
- Decreased perfusion pressure…hypotension, aortic regurgitation

Increased Oxygen Demand

- Aortic stenosis
- Severe HCM
- Thyrotoxicosis

DIAGNOSIS

- History
- Physical exam
- Electrocardiogram
- Exercise ECG test
- Exercise test with imaging
- Pharmacological stress test
- Coronary angiography

HISTORY: "ANGINA"

Quality

- Tightness
- Constriction
- Not pleuritic
- Radiation - jaws, arms
- Heaviness
- Not "stabbing"
- Dull, not sharp
- Association: SOB, sweat

Duration

- Steady, lasts minutes
- More than a few seconds
- Not usually ≥ 10-15 min.

Provocation

- Exertion, emotion
- Cold air
- Large meal

Relief

- Nitroglycerine - sec. to min.
- Rest

PHYSICAL EXAM

During ischemia

- ↑ BP
- ↑ HR
- Diaphoresis
- Transient mitral valve regurgitation (rare)
- Pulmonary rales (rare)

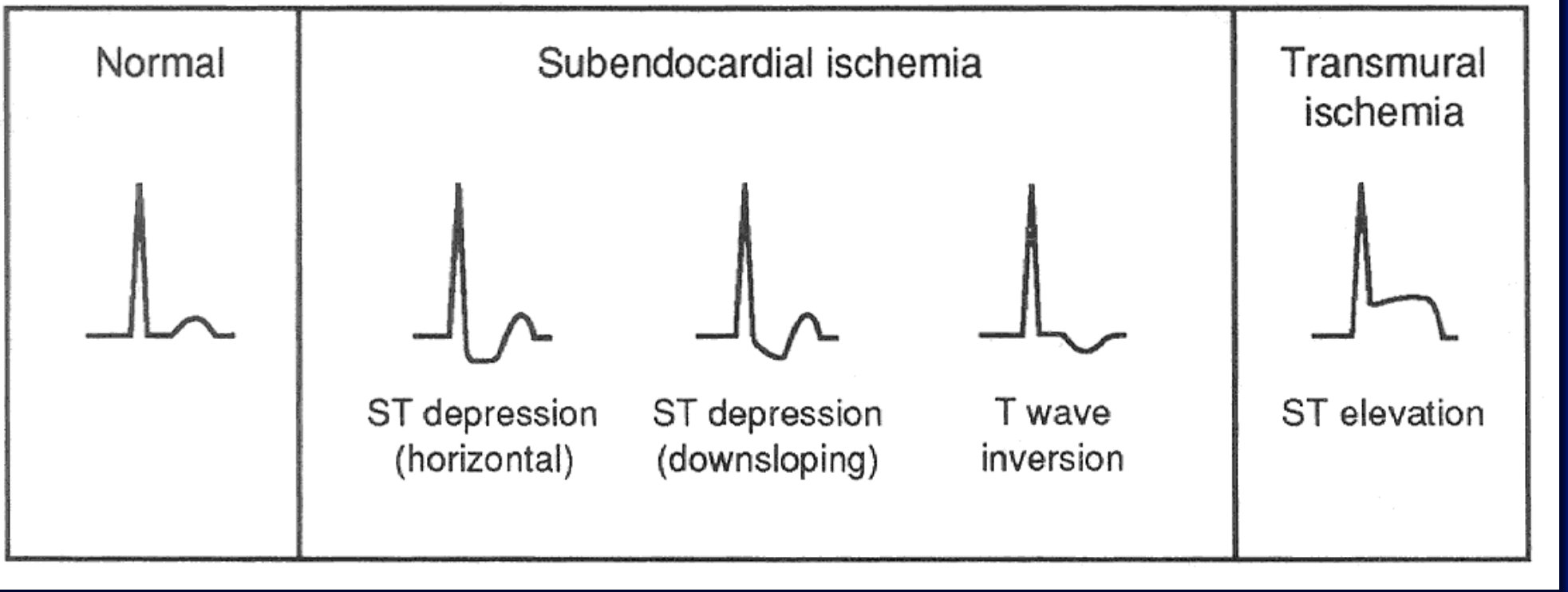
Not during ischemia

- Usually no abnormal findings
- Occasional associated issues:
  - aortic stenosis
  - HCM

  } — systolic murmur
  - aortic regurgitation - diastolic murmur

ELECTROCARDIOGRAM

- Usually shows change during an episode
- Typically transient ST-segment depression or T-wave flattening/inversion
- Rarely transient ST-segment elevation


Normal
Subendocardial ischemia
Transmural ischemia
ST depression (horizontal)
ST depression (downsloping)
T wave inversion
ST elevation

EXERCISE ECG STRESS TEST

Treadmill or bicycle exercise

Constant monitoring of:

12 lead ECG

heart rate

BP (periodically)

Graded increase in exercise until:

angina occurs with ECG changes… or

marked ischemia on ECG… or

target heart rate is reached… or

patient can no longer continue

STRESS TEST SIGNS: "SEVERE" CAD

- SX/ECG change occurs in 1st 3-6 min. of exercise or persists > 5 min. after
- Magnitude of ST depression ≥ 2mm
- Systolic BP falls during exercise
- High grade arrythmia - eg. Sustained ventricular tachycardia - occurs
- Cardiopulmonary limitations preclude exercise beyond 2-3 min.

EXERCISE TEST WITH IMAGING

Myocardial Perfusion Scintigraphy

- Nuclear tracer injected at peak exercise ⟶ image the heart
- Myocardium perfused by narrowed artery "takes" up less tracer than that served by normal coronaries
- Compare relative myocardial uptake at rest to that with exercise…
- Exercise "cold" spots that look normal at rest… viable heart muscle served by stenotic arteries
- Exercise cold spots that are also present at rest: dead heart muscle or very severe ↓ flow

EXERCISE TEST WITH IMAGING

Echocardiographic wall motion

- Image LV wall motion at rest
- Image immediately p̄ maximum stress
- Ischemic myocardium shows:
  - reduced systolic wall thickening
  - reduced systolic wall motion… hypokinesia/akinesia

PHARMACOLOGIC STRESS TEST: CHOICES

Adenosine - Thallium or Sestamibi:

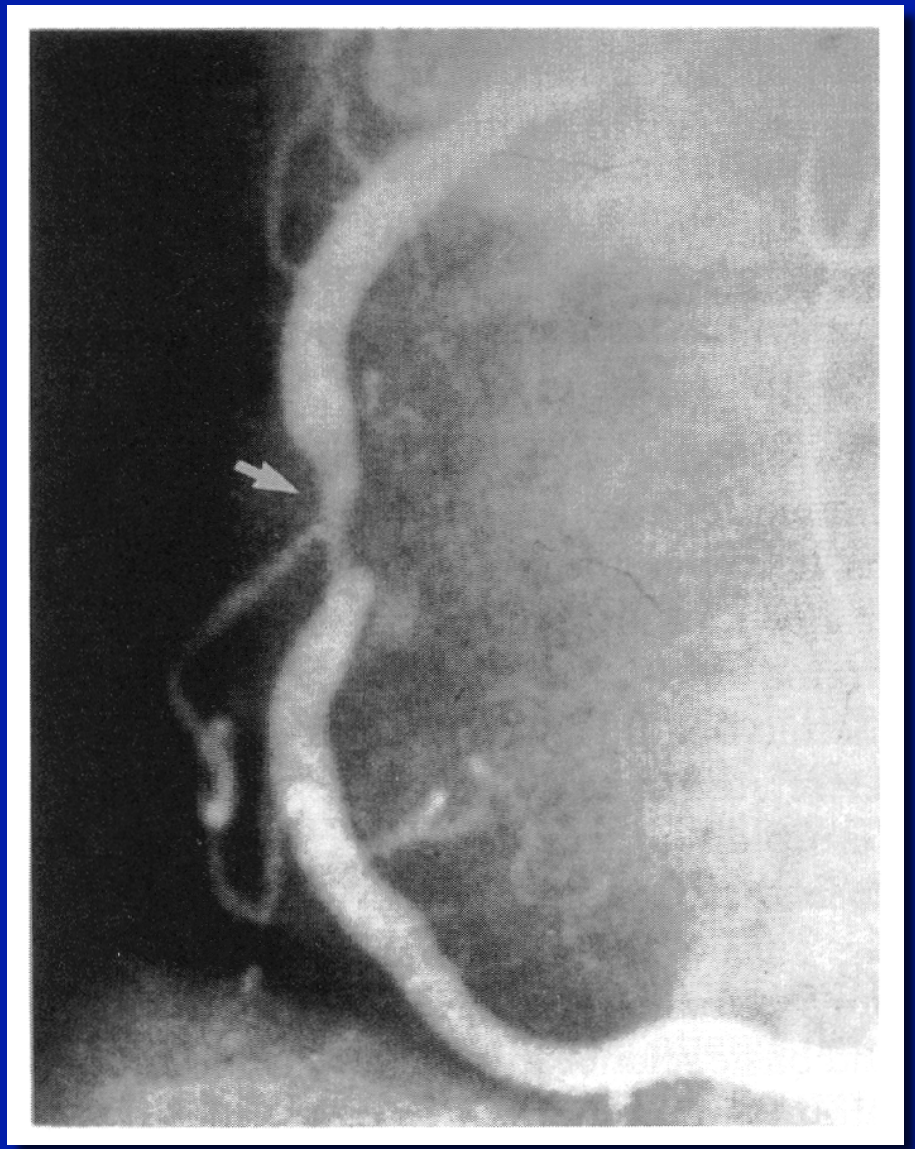
- Vasodilator
- Myocardial perfusion image
- Narrowed vessels have ↓ vasodilatory response c/w normal
- Before/after images → "relative" ↓ tracer uptake

Dobutamine Echocardiography

- Catecholemine stress mimics exercise
- Image for ischemia by ECG and wall motion analysis

CORONARY ANGIOGRAPHY

- Direct injection of radiopaque dye into coronary arteries
- Carries higher risk c/w noninvasive testing
- Most reliable method to obtain anatomical data
- When to do:
  - to establish Dx when uncertainty exists
  - to identify advanced CAD for potential revascularization c̄ PCI or CABG



TREATMENT STRATEGIES

- Prevent progression of atherosclerosis
- Prevent conversion of stable to unstable lesions
- Relieve symptoms to improve quality of life
- Prolong life

Prevent Progression of Atherosclerosis

- Identify / treat hyperlipidemia
- Identify / treat hypertension
- Identify / treat diabetes mellitus
- Identify / treat smoking
- Counteract obesity, sedentary lifestyle, depression, and other habits (e.g. cocaine)

Prevent Destabilization of Plaques

- Reduce shear stress
  - β-blocker
  - regular exercise
- Reduce thrombogenicity of blood
  - aspirin, clopidogrel
- Reduce vasoreactivity of vessels
  - β−blocker, nitrate, calcium blockers
  - no smoking
  - control lipids (statins)

RELIEVE SYMPTOMS OF ANGINA

Drug Class	Mechanism	Side Effects
β-blockers	↓ O_2 demand - ↓ Contractility ↑ O_2 Delivery - Slow HR	Fatigue/Depression Excess ↓ HR Bronchospasm Impotence
Long acting nitrates	↓ O_2 Demand - ↓ Preload ↑ O_2 Supply - ↑ Coronary Perfusion - ↓ Constriction	Headache Hypotension Reflex ↑ HR
Ca^{++} blockers	↓ Preload ↓ Wall stress ↓ HR (D,V) ↑ Perfusion/ ↓ Constriction	Headache Flushing Edema
Ranolazine	↓ Late phase Inward sodium	Dizziness, headache constipation, nausea

Antianginal Therapy

A. Nitrates

Medication	Dosage	Action	Duration
Sublingual NTG	0.3-0.6 mg	<5 min	<30 min
Aerosol NTG	0.4 mg	<5 mg	<30 min
NTG ointment (2%)	0.5-2.0 in	<60 min	6 h
Transdermal NTG	5-15 mg	30-60 min	8-14 h
Oral isosorbide	5-30 mg	15-30 min	3-6 h
Oral isosorbide (SR)	40 mg	30-60 min	6-10 h
Oral tetranitrate	10 mg	30 min	6-12 h

Antianginal Therapy

B. Calcium Channel Blockers

Medication	Dosage	Onset	Peak	Elimination	LA Form
Diltiazem	30-90 mg tid-qid	15 min	30 min	Renal/Hepatic	Yes
Nifedipine	10-30 mg tid-qid	<20 min	1-2 h	Hepatic	Yes
Verapamil	80-120 mg tid-qid	2 h	3-4 h	Hepatic	Yes
Amlodipine	2.5-10 mg qd-bid	<3 h	7-8 h	Hepatic	No
Isradipine	2.5-5.0 mg qd-bid	2 h	6-8 h	Hepatic	No
Nicardipine	20-30 mg tid	<20 min	1 h	Hepatic	No
Felodipine	2.5-10 mg qd	2 h	2.5-5 h	Hepatic	No

Antianginal Therapy

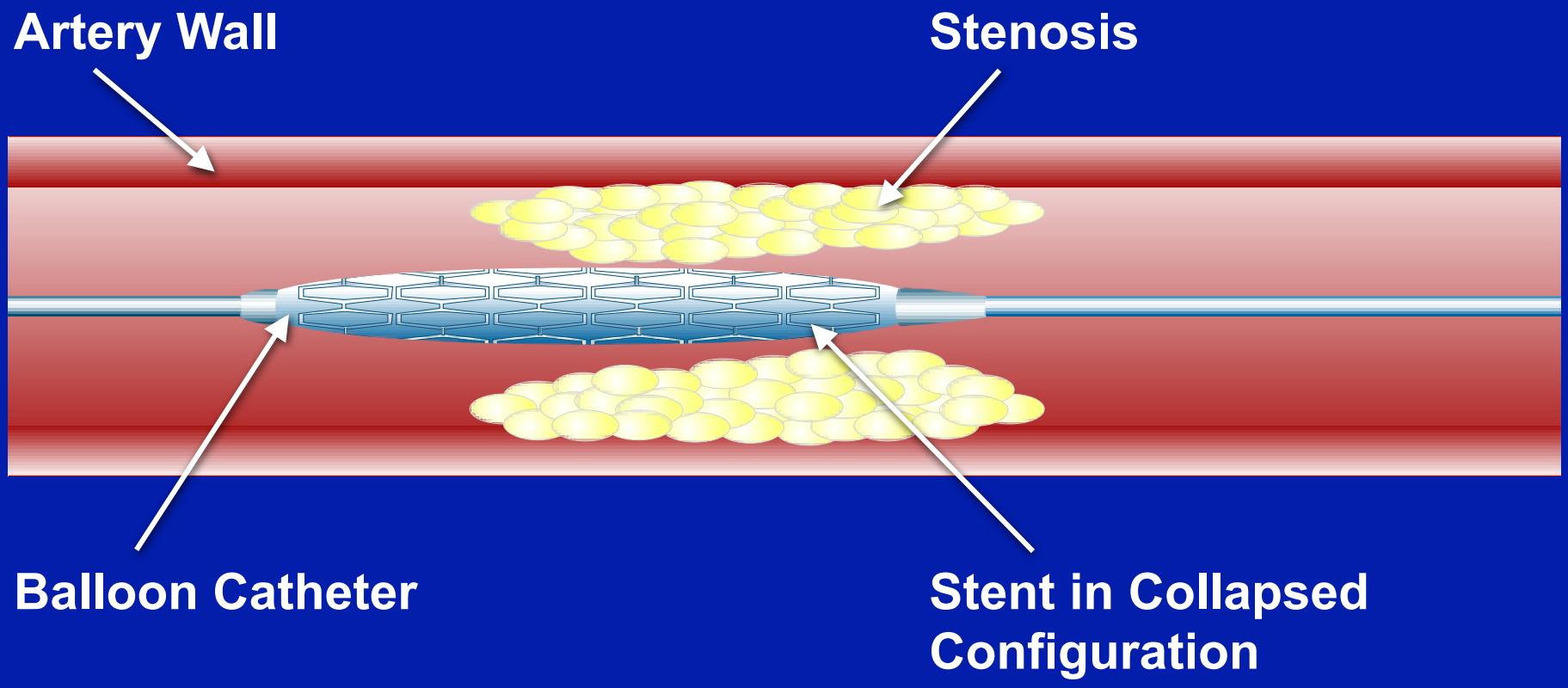
C. Beta Blockers

Medication	Dosage	Lipophilicity	ISA	Elimination	LA Form
Atenolol	25-100 mg qd	Low	No	Renal	No
Metaprolol	25-100 mg bid	Mod	No	Hepatic	Yes
Propanonol	10-40 mg qid	High	No	Hepatic	Yes
Pindolol	5-10 mg bid	Mod	Yes	Renal	No
Labetalol	100-200 mg bid	Low	No	Hepatic	No
Acebutolol	200-400 mg bid-tid	Low	No	Hepatic	Yes
Timolol	10-30 mg bid	Mod	No	Renal/Hepatic	No

PERCUTANEOUS CORONARY INTERVENTION

- Catheter based opening of fixed artery obstruction - main use is angina not / controlled with medical Rx.
- Multiple types of devices
  - Balloon
  - Stent
  - Rotoblator
  - Laser
  - Cutting catheter
  - Drug Eluting Stent
- Relieves angina caused by stenoses of > 50-60%… esp. when more severe
- Does not prevent acute MI in stable angina… issue is restenosis in 15-40% of pts.

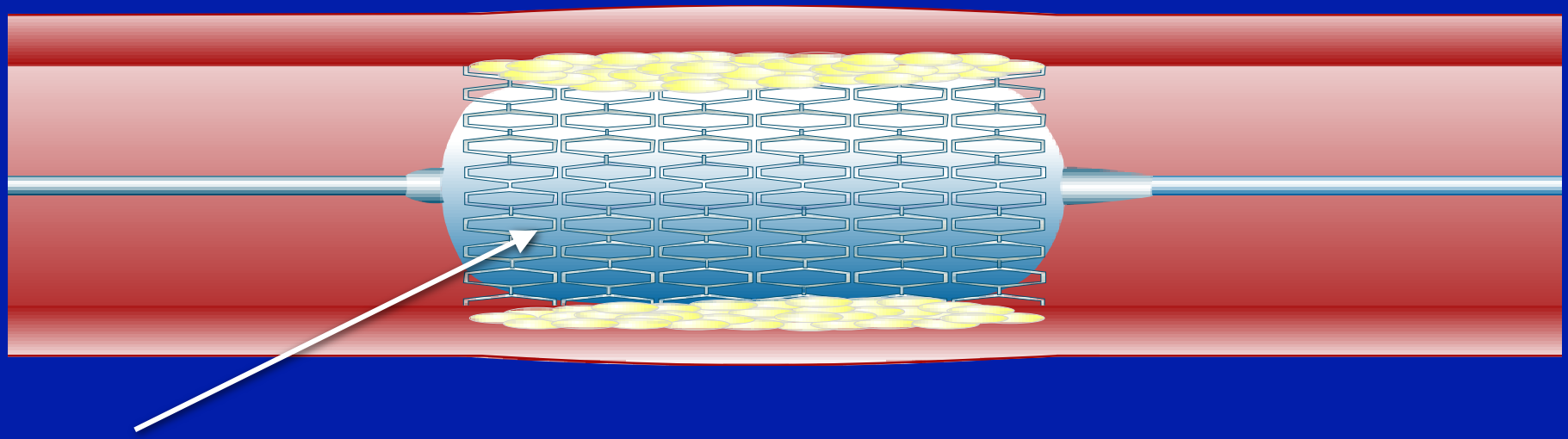
Chronic CAD



Stent in its original collapsed state, is advanced into the coronary stenosis on a balloon catheter.

 Lilly L, et al. *Pathophysiology of Heart Disease* 2007;164.

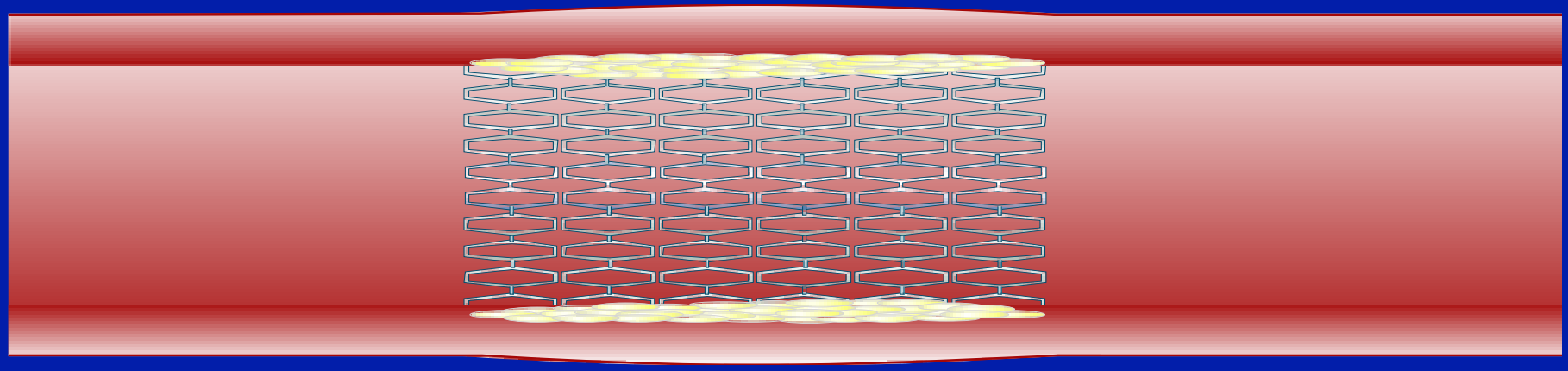
Chronic CAD



Balloon inflation to expand stent

Lilly L, et al. *Pathophysiology of Heart Disease* 2007;164.

Chronic CAD



The balloon is deflated and the catheter is removed from the body, leaving the stent permanently in place.

 Lilly L, et al. *Pathophysiology of Heart Disease* 2007;164.

Coronary Artery Bypass Surgery

- Surgically bypass arteries with advanced fixed obstruction
- Involves up front risk of death, stroke, sternal infection, post-op debility
- Relieves angina reliably
- Prolongs life in select anatomic subsets
- Disease can return in bypass grafts… arterial grafts preferred… left internal mammary artery to LAD

Chronic CAD

Relative Advantages of Coronary Revascularization Procedures

Percutaneous Coronary Interventions (PCI)

- Less invasive than CABG
- Shorter hospital stay and easier recuperation than CABG
- Superior to pharmacological therapy for relief of angina

Coronary Artery Bypass Graft Surgery (CABG)

- More effective for long-term relief of angina than PCI or pharmacologic therapy
- Most complete survival in patients with:
  - > 50% left main stenosis
  - 3-vessel CAD, especially if LV contractile function is impaired
  - 2-vessel disease with tight (>75%) LAD stenosis, especially if LV contractile function is impaired
  - Diabetes and multivessel disease

CAD, coronary artery disease; LV, left ventricle; LAD, left anterior descending coronary artery; MI, myocardial infarction.

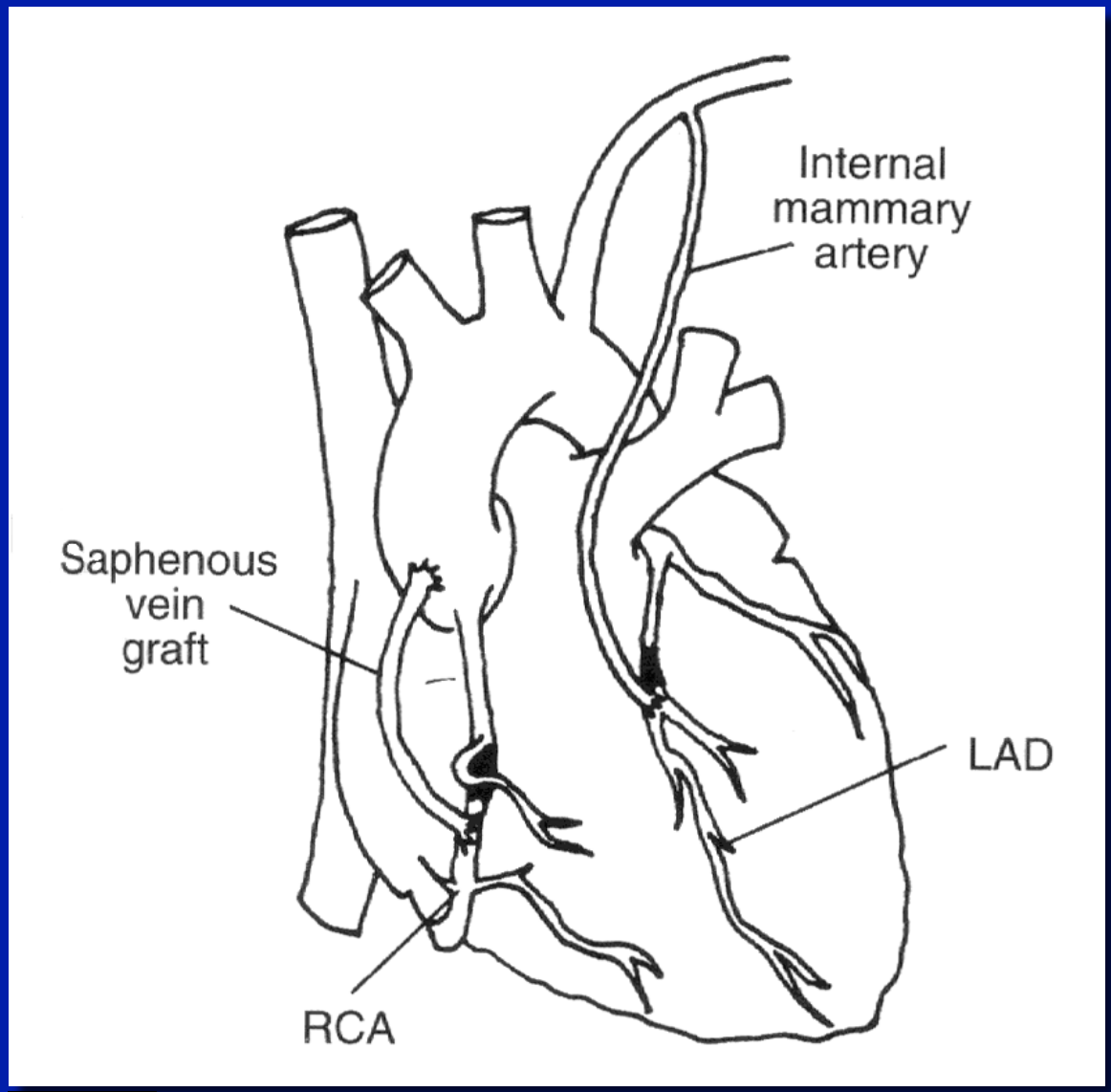
Lilly L, et al. *Pathophysiology of Heart Disease* 2007;166.

CHRONIC STABLE ANGINA: THERAPEUTIC BENEFITS

- Improves symptoms:
  - β-blocker
  - Ca^{++} blockers
  - PCI
  - Nitrates
  - Statins
  - CABG
- Prevents acute ischemic syndromes:
  - ASA
  - Lipid lowering agents
  - β-blocker
  - Stop smoking
  - ? ACE inhibitors
- Prolongs life
  - CABG in:
  - Lipid lowering drugs

→ Left main stenosis
signif. 3 vessel disease
2 vessel with prox. LAD

← Especially if
↓ LV function
and/or
(+) stress test



 Lilly. Pathophysiology of Heart Disease, 4th Ed. Lippincott Williams, 2007. Page 165

PROGNOSIS

MAJOR PREDICTORS:

- Advanced age
- LV dysfunction
- Extent of CAD

Extent of CAD	Annual mortality
1 vessel	< 4%
2 vessel	7 - 10%
3 vessel	10 - 12%
Left main	15 - 25%

Coronary Artery Disease Prognostic Index

Extent Of CAD	5 - Year Survival Rate (%)
1 - vessel disease, 75%	93
>1 - vessel disease, 50% to 74%	93
1 - vessel disease, ≥ 95%	91
2 - vessel disease	88
2 - vessel disease, both ≥ 95%	86
1 - vessel disease, ≥ 95% proximal LAD	83
2 - vessel disease, ≥ 95% LAD	83
2 - vessel disease, ≥ 95% LAD	79
3 - vessel disease	79
3 - vessel disease, ≥ 95% in at least 1	73
3 - vessel disease, 75% proximal LAD	67
3 - vessel disease, ≥ 95% proximal LAD	59

Reference: JACC 1999; 33: 2092-197

CHRONIC STABLE ANGINA

- Development
- Clinical definitions
- Myocardial oxygen supply and demand
- Pathophysiology
- Diagnosis
- Treatment strategies
- Prognosis