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CARDIOVASCULAR SEQUENCE

Coronary Artery Disease: Chronic Disease

Kim A. Eagle, M.D.
University of Michigan Health System

Fall 2012
Kim A. Eagle, MD

Director
University of Michigan
Cardiovascular Center

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**

- Intimal thickening
- Initial Lesion
  - From 1st decade of life
  - Clinically silent

**TYPE II**

- Foam cells
- Fatty Streak
  - From 1st decade of life
  - Growth by lipid accumulation
  - Clinically silent
**AHA CLASSIFICATION**

**TYPE III**
- Foam cell
- Lipid

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

**TYPE IV**
- Foam cell
- Lipid

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

**TYPE V**
- Foam cell
- Lipid
- Fibrous cap

**Fibroatheroma**
- Lipid core
- Fibrotic layer
- Smooth muscle cells
- Clinically silent or overt
TYPE VI

Plaque hemorrhage

Lipid

Foam cell

Fibrous cap

Coronary thrombus

Erosion or disruption of fibrous cap

Platelet attachment

Fibrin network

Complicated Plaque

- Surface defect
- Surface clot
- Hemorrhage in plaque
- Luminal thrombus
- From 4th decade
- Clinically overt
Classic Angina:
Transient discomfort or pain sensation occurring 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.
1. Provoked by physical or mental stress
2. Associated with ST-segment depression
3. Lasts $\leq$ 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
Stable Angina

- Lumen narrowed by plaque
- Inappropriate vasoconstriction
Chronic CAD

Unstable Angina

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

Platelets

Thrombus
Variant Angina

- No overt plaques
- Intense vasospasm
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
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
    - $\alpha$ - adrenergic receptors → vasoconstriction
    - $\beta$ - 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

Maximal Coronary Flow

Resting Coronary Flow

Maximum Coronary Flow

25%  50%  75%  100%
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
  – aortic regurgitation - diastolic murmur

} — systolic 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

ST depression (horizontal) ST depression (downsloping) T wave inversion

Transmural ischemia

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 arrhythmia - 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 after 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 c 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
  - \( \beta \)-blocker
  - regular exercise

- Reduce thrombogenicity of blood
  - aspirin, clopidogrel

- Reduce vasoreactivity of vessels
  - \( \beta \)-blocker, nitrate, calcium blockers
  - no smoking
  - control lipids (statins)
# RELIEVE SYMPTOMS OF ANGINA

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-blockers</strong></td>
<td>↓ ( O_2 ) demand</td>
<td>Fatigue/Depression</td>
</tr>
<tr>
<td></td>
<td>- - ↓ Contractility</td>
<td>Excess ↓ HR</td>
</tr>
<tr>
<td></td>
<td>↑ ( O_2 ) Supply</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>- - ↑ Coronary Perfusion</td>
<td>Impotence</td>
</tr>
<tr>
<td></td>
<td>- - ↓ Constriction</td>
<td></td>
</tr>
<tr>
<td>Long acting</td>
<td>↓ ( O_2 ) Demand</td>
<td>Headache</td>
</tr>
<tr>
<td>nitrates</td>
<td>- - ↓ Preload</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>↑ ( O_2 ) Supply</td>
<td>Reflex ↑ HR</td>
</tr>
<tr>
<td></td>
<td>- - ↑ Coronary Perfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- - ↓ Constriction</td>
<td></td>
</tr>
<tr>
<td><strong>Ca++ blockers</strong></td>
<td>↓ Preload</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>↓ Wall stress</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>↓ HR (D,V)</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>↑ Perfusion/Constriction</td>
<td></td>
</tr>
<tr>
<td><strong>Ranolazine</strong></td>
<td>↓ Late phase</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Inward sodium</td>
<td>constipation, nausea</td>
</tr>
</tbody>
</table>
## ANTIANGINAL THERAPY

### A. NITRATES

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Action</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual NTG</td>
<td>0.3-0.6 mg</td>
<td>&lt;5 min</td>
<td>&lt;30 min</td>
</tr>
<tr>
<td>Aerosol NTG</td>
<td>0.4 mg</td>
<td>&lt;5 mg</td>
<td>&lt;30 min</td>
</tr>
<tr>
<td>NTG ointment (2%)</td>
<td>0.5-2.0 in</td>
<td>&lt;60 min</td>
<td>6 h</td>
</tr>
<tr>
<td>Transdermal NTG</td>
<td>5-15 mg</td>
<td>30-60 min</td>
<td>8-14 h</td>
</tr>
<tr>
<td>Oral isosorbide</td>
<td>5-30 mg</td>
<td>15-30 min</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Oral isosorbide (SR)</td>
<td>40 mg</td>
<td>30-60 min</td>
<td>6-10 h</td>
</tr>
<tr>
<td>Oral tetranitrate</td>
<td>10 mg</td>
<td>30 min</td>
<td>6-12 h</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosage</td>
<td>Onset</td>
<td>Peak</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>30-90 mg tid-qid</td>
<td>15 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10-30 mg tid-qid</td>
<td>&lt;20 min</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Verapamil</td>
<td>80-120 mg tid-qid</td>
<td>2 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5-10 mg qd-bid</td>
<td>&lt;3 h</td>
<td>7-8 h</td>
</tr>
<tr>
<td>Isradipine</td>
<td>2.5-5.0 mg qd-bid</td>
<td>2 h</td>
<td>6-8 h</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-30 mg tid</td>
<td>&lt;20 min</td>
<td>1 h</td>
</tr>
<tr>
<td>Felodipine</td>
<td>2.5-10 mg qd</td>
<td>2 h</td>
<td>2.5-5 h</td>
</tr>
</tbody>
</table>
## Antianginal Therapy

### C. Beta Blockers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Lipophilicity</th>
<th>ISA</th>
<th>Elimination</th>
<th>LA Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>25-100 mg qd</td>
<td>Low</td>
<td>No</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Metaprolol</td>
<td>25-100 mg bid</td>
<td>Mod</td>
<td>No</td>
<td>Hepatic</td>
<td>Yes</td>
</tr>
<tr>
<td>Propanolol</td>
<td>10-40 mg qid</td>
<td>High</td>
<td>No</td>
<td>Hepatic</td>
<td>Yes</td>
</tr>
<tr>
<td>Pindolol</td>
<td>5-10 mg bid</td>
<td>Mod</td>
<td>Yes</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Labetalol</td>
<td>100-200 mg bid</td>
<td>Low</td>
<td>No</td>
<td>Hepatic</td>
<td>No</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>200-400 mg bid-tid</td>
<td>Low</td>
<td>No</td>
<td>Hepatic</td>
<td>Yes</td>
</tr>
<tr>
<td>Timolol</td>
<td>10-30 mg bid</td>
<td>Mod</td>
<td>No</td>
<td>Renal/Hepatic</td>
<td>No</td>
</tr>
</tbody>
</table>
Percutaneous Coronary Intervention

- Catheter based opening of fixed artery obstruction - main use is angina not controlled with medical Rx.
- Multiple types of devices:
  - Balloon
  - Laser
  - Stent
  - Cutting catheter
  - Rotoblator
  - 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.
Stent in its original collapsed state, is advanced into the coronary stenosis on a balloon catheter.
Chronic CAD

Balloon inflation to expand stent

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

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

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

**Major Predictors:**

- Advanced age
- LV dysfunction
- **Extent of CAD**
  - 1 vessel: < 4%
  - 2 vessel: 7 - 10%
  - 3 vessel: 10 - 12%
  - Left main: 15 - 25%
## Coronary Artery Disease Prognostic Index

<table>
<thead>
<tr>
<th>Extent of CAD</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - vessel disease, 75%</td>
<td>93</td>
</tr>
<tr>
<td>&gt;1 - vessel disease, 50% to 74%</td>
<td>93</td>
</tr>
<tr>
<td>1 - vessel disease, ≥ 95%</td>
<td>91</td>
</tr>
<tr>
<td>2 - vessel disease</td>
<td>88</td>
</tr>
<tr>
<td>2 - vessel disease, both ≥ 95%</td>
<td>86</td>
</tr>
<tr>
<td>1 - vessel disease, ≥ 95% proximal LAD</td>
<td>83</td>
</tr>
<tr>
<td>2 - vessel disease, ≥ 95% LAD</td>
<td>83</td>
</tr>
<tr>
<td>2 - vessel disease, ≥ 95% LAD</td>
<td>79</td>
</tr>
<tr>
<td>3 - vessel disease</td>
<td>79</td>
</tr>
<tr>
<td>3 - vessel disease, ≥ 95% in at least 1</td>
<td>73</td>
</tr>
<tr>
<td>3 - vessel disease, 75% proximal LAD</td>
<td>67</td>
</tr>
<tr>
<td>3 - vessel disease, ≥ 95% proximal LAD</td>
<td>59</td>
</tr>
</tbody>
</table>

Reference: JACC 1999; 33: 2092-197
CHRONIC STABLE ANGINA

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