CORONARY ARTERY DISEASE

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Control of coronary blood flow

Coronary autoregulation:-

- determinants of myocardial oxygen consumption = heart rate, systolic pressure (or myocardial wall stress), left ventricular contractility

- when determinants of myocardial oxygen consumption constant →regional coronary blood flow remains constant

- coronary reserve = ability to increase coronary flow in response to pharmacologic vasodilation

Control of coronary tone:-

1. **Endothelial-dependent factors eg. nitric oxide, endothelium-dependent hyperpolarizing factor, prostacyclin, endothelin**
2. **Local physical factors:**
   - **a) pressure – myogenic regulation (vessels relax when distending pressure decrease, and constrict when distending pressure increase)**
     - **during systole, compression of microcirculatory vessels → coronary arterial inflow decrease as venous flow increase**
     - **increase preload reduce coronary driving pressure and subendocardial perfusion**
   - **b) flow – flow-mediated resistance (shear stress) → dilation**
     - **subendocardial flow occurs in diastole (decrease when coronary pressure < 40mmHg). Subepicardial flow occurs throughout cardiac cycle (decrease when coronary pressure < 25 mmHg) →vulnerability of subendocardium to ischemia in coronary stenosis**
3. **Mediators of coronary resistance eg. adenosine, ATP-sensing K+ channels, hypoxia, acidosis, serotonin, thromboxane, ADP**
4. **Sympathetic and parasympathetic neural control**

Myocardial ischemia

= imbalance between myocardial oxygen supply and demand

Increased myocardial oxygen demand (= demand ischemia):

eg. exercise, tachycardia, stress, fever

Decreased myocardial oxygen supply (= supply ischemia):

eg. reduced coronary blood flow and reserve, coronary vascular resistance, coronary occlusion

Types of coronary artery disease

(I) ***Acute coronary syndromes:***

1. ST elevation myocardial infarction (STEMI)
2. Non-ST elevation myocardial infarction (NSTEMI = unstable angina + elevated cardiac enzymes)
3. Unstable angina

(II) ***Chronic coronary artery disease:***

1. Stable angina pectoris
2. Prinzmetal (variant) angina
3. Syndrome X (microvascular angina)
4. Silent myocardial ischemia

ST elevation myocardial infarction (STEMI)

WHO criteria for diagnosis of STEMI (≥2 of followings):

1. chest pain and history
2. evolutionary ST elevation on serially obtained electrocardiogram
3. serially cardiac enzymes elevation:
   a) creatine kinase (CK): increase 4-6 hours after STEMI and decline to normal within 2-3 days.
   False positive: muscle disease, alcohol intoxication, diabetes, trauma, vigorous exercise, convulsion, intramuscular injection, pulmonary embolism etc.
   b)isoenzymes(CKMB): significant if >5% that of CK.
   False positive: myocarditis, trauma, shock, catheterization, heart surgery etc.

c) troponin: increase 3 hours after STEMI and persist for 7-10 days

Troponin elevation not due to acute myocardial infarction

- acute or chronic heart failure
- acute pulmonary embolism
- aortic dissection
- cardiac trauma
- cardiotoxic chemotherapy
- pericarditis/myocarditis
- sepsis/critically ill patients
- strenuous exercise
- valvular heart disease
- rhabdomyolysis
- biochemical false positive

Killip classification of acute myocardial infarction

		mortality
1	no sign of heart failure	6%
2.	bibasilar rales	17%
3.	acute pulmonary edema	38%
4.	cardiogenic shock	81%

Pathophysiology of ST elevation myocardial infarction

1. **Almost all STEMI result from coronary atherosclerosis, with superimposed coronary thrombosis = plague rupture**

   - plague rupture → completely occlusive thrombus →STEMI
   → less obstructive thrombus →
   a) NSTEMI (with elevated cardiac enzymes)
   b) unstable angina (without elevated cardiac enzymes)

   - risk of plague rupture depend primarily on plague morphology (erosion, intraplague hemorrhage, lipid-rich plague with thin fibrous cap and inflammatory cells), less on plague size, and not on severity of stenosis.

   - fibrosis hardens and stabilized plague, inflammation degrades fibrous cap to rupture, and coagulation factors in circulating blood and within atherosclerotic lesion also affect plague rupture.

2. Coronary atherosclerosis without superimposed coronary thrombosis and plague rupture

3. Without atherosclerosis eg. Prinzmetal variant angina (due to prolonged severe vasospasm with marked decrease myocardial oxygen supply), arteritis, trauma to coronary arteries, emboli, congenital coronary artery anomalies, imbalanced myocardial oxygen supply and demand (eg. aortic stenosis and insufficiency, prolonged hypotension, thyrotoxicosis etc.)

plague rupture precipitated by:

- high plague lipid content
- local inflammation
- coronary artery constriction at site of plague
- local shear stress force
- platelet activation
- status of coagulation system
- circadian variation (increased platelet aggregatibility, myocardial oxygen demand, blood pressure, heart rate, emotional stress, physical exertion in early morning)

Triggers of vascular inflammation

- ***Noninfectious factors*** eg. oxidized lipoproteins, diabetes, hypertension (mechanical stress), smoking, sympathoadrenal activation (physical, emotional stress), neuroendocrine factors (increased angiotensin II), hyperhomocysteinemia, renal insufficiency (uremic factors), other inflammatory mediators (cytokines, oxidants)

- ***Infectious factors*** eg. bacteria, virus

Pathological classification of myocardial infarction

1. ***Transmural infarction*** = myocardial necrosis involving full thickness (or nearly) of ventricle, usually due to occlusive thrombus
2. ***Subendocardial infarction (non-transmural)*** = myocardial necrosis involving subendocardium, intramural myocardium or both (but not epicardium), usually due to severely narrowed but still patent coronary artery

Clinical features of ST elevation myocardial infarction

1. ***Predisposing factors:***
   - unusual heavy exertion or mental stress, anger
   - accelerating or rest angina may culminate as STEMI
   - infections, hypoxemia, pulmonary embolism, hypoglycemia, trauma, neurologic (transient ischemic attack or stroke) etc.

2. ***Circadian periodicity:***
   peak incidence of STEMI = 6 am to 12 noon, due to physiological and biochemical alternations eg. rise in plasma catecholamine and cortisol, increased platelet aggregatibility in early morning

3. ***Nature of chest pain:***
   - mostly severe and prolonged (> 30 minutes)
   - may associate with : anxiety, distress, skin pallor, cold perspiration, acute heart failure, marked weakness, syncope, nausea vomiting. sense of impending doom etc.

Complications of ST elevation myocardial infarction

1. **Hemodynamic disturbances:**

   impaired ventricular performance, cardiogenic shock (>30 minutes, systolic < 80mmHg hypotension), mechanical heart failure (eg. free wall rupture, pseudoaneurysm, rupture of interventricular septum, papillary muscle rupture)
2. **Arrhythmias**
3. **Postinfarction angina and reinfarction**
4. **Pericardial effusion and pericarditis (usually 1-6 weeks post STEMI. More common in anterior infarction with larger infarct size and heart failure)**
5. **Dressler syndrome = postmyocardial infarction syndrome (usually 1-8 weeks post STEMI. Symptoms = fever, leukocytosis, malaise, chest pain, pericardial effusion)**
6. **Venous thrombosis and pulmonary embolism**
7. **Left ventricular aneurysm**
8. **Left ventricular thrombus and embolism**

Sequelae of ST elevation myocardial infarction

1. ***Left ventricular dysfunction:***
   - reduced cardiac output, blood pressure, contractility
   - abnormal contraction (eg. dyssynchrony, hypokinesis, akinesis, dyskinesis)

2. ***Circulatory dysfunction:***

   STEMI → increased preload and afterload → decreased stroke volume and increased myocardial oxygen consumption → poor circulation

3. ***Ventricular remodeling:***

   = changes in left ventricular size, shape and thickness of infarcted and noninfarcted regions

- ***Right ventricular infarction:***
  - ST elevation in leads V4R, V5R, V6R
  - Kussmaul sign (inspiration → increased jugular venous pressure)
  - Pulsus paradoxus (inspiration → decreased systolic pressure > 10 mmHg)

- ***Myocardial stunning*** = prolonged post ischemic contractile dysfunction even after ischemic insult itself has resolved

- ***Hibernating myocardium*** = poorly or noncontracting viable myocardium due to chronic reduction in myocardial blood supply following episodes of reversible ischemia perfused by stenosed artery

Non-ST elevation myocardial infarction and unstable angina

Diagnosis of NSTEMI and unstable angina:-

History – chest pain

prior history of angina and coronary artery disease (80%)

age > 60 years, male

> 2 cardiac risk factors, especially diabetes

Physical examination: hypotension, hemodynamic compromise, heart failure, pulmonary rale

Electrocardiogram: ST ischemic changes, left bundle branch block

Cardiac enzymes: elevated CK, CKMB or troponin (→NSTEMI). If no elevation → unstable angina

Braunwald clinical classificatin of unstable angina

Severity:

I new onset severe or accelerated angina, no rest pain

II subacute angina at rest (within past month but not within preceding 48 hours)

III acute angina at rest (within 48 hours)

Clinical circumstances:

A (secondary angina) – develop due to precipitating noncoronary factors eg. anemia, infection,arrhythmias

B (primary angina)-develop without precipitating factors

C (postinfarction angina) – develop within 2 weeks after acute myocardial infarction

Pathophysiology of non-ST elevation myocardial infarction and unstable angina

- Mostly result from rupture or erosion of atherosclerotic plague, with superimposed nonocclusive thrombus. There is severe coronary obstruction (but not total occlusion) of coronary artery.
- Thrombosis or embolism
- Platelet aggregation:

platelet (glycoprotein Ib receptor) adhere to endothelium (von Willebrand factor)

↓

platelet activation

↓

release of thromboxane A2, serotonin

↓

platelet glycoprotein IIb/IIIa receptors

+ fibrinogen ↓

platelet plug formation

- Simultaneous with platelet plug formation, plasma coagulation system is activated, forming coronary thrombi
- Dynamic obstruction due to : 1. coronary spasm
  2. constriction of intramural coronary resistance vessels
  3. local vasoconstrictors eg. thromboxane 4. endothelial dysfunction 5. adrenergic stimuli
- Progressive luminal narrowing due to ahterosclerosis
- inflammation
- Secondary causes (with worse prognosis than primary causes) eg. imbalanced myocardial oxygen supply and demand caused by: tachycardia, fever, thyrotoxicosis, hypertension, aortic stenosis, anemia, hypoxemia, hyperviscosity state, hypotension etc.

Clinical features of non-ST elevation myocardial infarction and unstable angina

- Chest pain at rest (or minimal exertion) lasting >20 minutes
- New onset (within 1 month)
- Crescendo pattern (ie. more severe, prolonged or frequent angina than previously)
- May associate with: pale cool skin, tachycardia, hypotension, cold sweating, heart failure etc.
- Myocardial necrosis with elevated cardiac enzymes may (=NSTEMI) or may not(= unstable angina) occur, due to obstruction of small, distal coronaries by microemboli of thrombus or plague debris from a more proximal lesion

Chronic coronary artery disease

1. Stable angina pectoris:

- mostly result from obstruction of coronary artery by atherosclerotic plague. Usually not severe nor total occlusion
- chest discomfort (usually not pain) caused by myocardial ischemia (=imbalance between myocardial oxygen supply and demand), especially on exertion or stress, with or without radiation to arms, upper abdomen, back, jaw, shoulder, back etc.
- anginal equivalents (= symptoms of myocardial ischemia other than chest pain) eg. dyspnea, faintness, fatigue, cold sweating etc.
- relieved within 5-15 minutes by rest or nitroglycerin

Canadian cardiovascular society classification of angina pectoris

Class	I	no angina with ordinary activity
	II	slight limitation with ordinary activity
	III	marked limitation with ordinary activity
	IV	angina at rest

2. Prinzmetal (variant) angina:

- ***Coronary spasm*** (= abnormal contraction of coronaries resulting in myocardial ischemia, associated with ST elevation (total or subtotal occlusion) or mostly ST depression(diffuse occlusion))may lead to variant angina, effort angina, unstable angina, acute myocardial infarction, sudden death.
- Occurs most often at rest, particularly from midnight to early morning
- ***Risk factors*** = cigarette smoking (major), age, postmenopausal, hyperlipidemia, hypertension, diabetes
- ***Precipitating factors*** = physical or mental stress, exposure to cold, Valsalva maneuver and hyperventilation, magnesium deficiency, drugs eg. catecholamine, parasympathetic agents, ergonovine, serotonin, histamine, beta blockers, withdrawal from long-term nitroglycerin, cocaine, nicotine and alcohol
- ***Circadian variation*** due to circadian production of various hormones eg. autonomic hormones, vasopressin, melatonn, growth hormone, insulin, cortisol
- Any form of invasive therapeutic procedure such as stenting or bypass grafting is contraindicated unless severe ahterosclerotic coronary disease is also present.

3. ***Syndrome X (microvascular angina):***

= angina with normal coronaries

- due to microvascular dysfunction (inadequate coronary reserve), abnormal pain sensitivity or endothelial dysfunction

4. ***Silent myocardial ischemia:***

= asymptomatic with obstructive coronary artery disease (obstruction may be severe)

- due to decreased pain sensitivity, autonomic neuropathy (diabetes) etc.

Management of coronary artery disease

(I) ***ST elevation myocardial infarction (STEMI):***

1. ***Reperfusion of myocardial infarction:***

early reperfusion shortens duration of coronary occlusion, and minimizes short and long term complications

a) *intravenous thrombolysis (within 12 hours)*-

contraindications:

- **previous hemorrhagic stroke (or other strokes within 1 year)**
- **intracranial tumor**
- **active internal bleeding**
- **suspected aortic dissection**

relative contraindications:

- **uncontrolled hypertension**
- **history of strokes**
- **recent trauma (within 2-4 weeks) or major surgery (<3 weeks)**
- **recent internal bleeding (within 2-4 weeks)**
- **pregnancy, active peptic ulcer**

b) Primary angioplasty:

preferable, because of higher patency rate (85-90% for intervention vs 65% for thrombolysis).

If chest pain < 3 hours → thrombolysis or angioplasty
If chest pain > 3 hours or diagnosis doubtful → angioplasty

c) Surgical reperfusion **(within 4-6 hours):**

indication:

- **persistent or recurrent chest pain or hemodynamic instability despite thrombolysis or angioplasty**
- **high risk coronary anatomy**
- **mechanical complications such as ventricular septal rupture, severe mitral regurgitation**

2. Antithrombotic and antiplatelet drugs:

to prevent further thrombosis eg. aspirin, heparin, clopidogrel, ticlopidine, glycoprotein IIa/IIIb inhibitor

3. Antianginal drugs:

to reduce myocardial oxygen demand eg.beta blocker, nitrate, calcium antagonist, ACE inhibitor

(II) Non-ST elevation myocardial infarction and unstable angina:

- early angioplasty within 48 hours (with concomitant use of glycoprotein IIb/IIIa inhibitor) is superior to conservative therapy
- antithrombotic and antiplatelet drugs
- antianginal drugs

(III) Chronic coronary artery disease:

- treat precipitating factors and lifestyle modification
- antithrombotic and antiplatelet drugs
- antianginal drugs
- If refractory or ischemic despite medical therapy → angioplasty

Pharmacology

1. ***Antithrombotic and antiplatelet drugs:***

Aspirin:

mechanism- anti-platelet aggregation
- decreased CRP, macrophage colony-stimulating factors
- improve endothelial function by inhibiting release of cyclooxygenase-dependent endothelium-derived constricting factors

side effects: gastrointestinal bleeding, allergy

Clopidogrel: reduce platelet aggregation and blood viscosity

Ticlopidine: side effects: neutropenia, thrombocytopenia

Glycoprotein IIb/IIIa inhibitor eg. Abciximab

mechanism: inhibit platelet aggregation by binding to platelet glycoprotein IIb/IIIa receptor

side effects: thrombocytopenia, increased bleeding

2. Beta blocker:

mechanism- reduce cardiac output, heart rate, blood pressure, infarct size, catecholamine, myocardial oxygen consumption

side effects: bradycardia, heart block, bronchoconstriction, fatigue, mental depression, nightmare, gastrointestinal upset, sexual dysfunction, skin reaction etc.

contraindications: heart rate < 60 beats/min
systolic blood pressure < 100 mmHg
signs of peripheral hypoperfusion
heart block
asthma and severe chronic lung disease
severe peripheral vascular disease

3. ACE inhibitor: vasodilating, antiinflammatory, antiproliferative

mechanism: reduce hypertrophy, atherosclerosis, plague rupture and thrombosis, sympathetic activity
- improve endothelial vasomotor function
- improve hemodynamic, remodeling, heart failure

contraindications: hypotension, pregnancy, hypersensitivity

side effects: hypotension, intolerable cough, angioedema

4. Nitrate:

mechanism: vasodilator that reduce preload, infarct size and complication, improve coronary blood flow, decrease myocardial oxygen consumption, dilatation of epicardial stenoses

side effects: headache, flushing, hypotension, lethargy, nitrate intolerance, methemoglobinemia(if very high dose)

5. Calcium antagonist:

- for NSTEMI and unstable angina, and chronic coronary disease
- not recommended in ST elevation myocardial infarction (may be given for relief of ischemia or rapid ventricular response in atrial fibrillation if beta blocker ineffective or contraindicated)

mechanism: decrease myocardial oxygen demand

- relaxation of vascular smooth muscle
- vasodilator
- reduce preload and afterload
- decrease thrombus formation and platelet aggregation

side effects: headache, dizziness, palpitation, flushing, hypotension, leg edema, gastrointestinal upset

6. Statin:

- Lipid lowering
- Stabilize plagues by increasing collagen in plague, decreasing macrophage activation, increasing metalloproteinases (prevent matrix degeneration), modulating immune function