ACS pathophysiology: an Update

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המרכס הרפואים הדסה ירושלים

השדולה: למתמטים בקרדיולוגיה

קורסיים, 2 נובמבר 2010
Atherothrombosis is the Leading Cause of Death Worldwide

- AIDS: 5.1%
- Pulmonary Disease: 6%
- Injuries: 9%
- Cancer: 12%
- Infectious Disease: 19%
- Atherothrombosis*: 28%

*Mortality (%)

*Ischemic heart disease, cerebrovascular disease, inflammatory heart disease and hypertensive heart disease
†Worldwide defined as Member States by WHO Region (African, Americas, Eastern Mediterranean, European, South-East Asia and Western Pacific)
Atherothrombosis: a systemic disease

~2,000

~20,000
Evolution of the atherosclerotic plaque
Initiation, progression, and complication of human coronary atherosclerotic plaque
History of biomarkers and the definition of acute myocardial infarction (AMI).
New (universal) MI definition

• Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

• Type 2: MI secondary to ischemia due to oxygen demand:supply imbalance (coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension)

• Type 3: Sudden unexpected cardiac death accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

• Type 4a: MI associated with PCI
• Type 4b: MI associated with stent thrombosis (definite)

• Type 5: Myocardial infarction associated with CABG
Elevations of troponin in the absence of overt IHD

<table>
<thead>
<tr>
<th>Table 2 Elevations of troponin in the absence of overt ischemic heart disease</th>
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<tbody>
<tr>
<td>Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.</td>
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<tr>
<td>Congestive heart failure—acute and chronic</td>
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<td>Aortic dissection</td>
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<td>Aortic valve disease</td>
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<td>Hypertrophic cardiomyopathy</td>
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<td>Tachy- or bradyarrhythmias, or heart block</td>
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<td>Apical ballooning syndrome</td>
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<td>Rhabdomyolysis with cardiac injury</td>
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<td>Pulmonary embolism, severe pulmonary hypertension</td>
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<td>Renal failure</td>
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<td>Acute neurological disease, including stroke or subarachnoid haemorrhage</td>
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<td>Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma</td>
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<td>Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis</td>
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<tr>
<td>Drug toxicity or toxins</td>
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<td>Critically ill patients, especially with respiratory failure or sepsis</td>
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<td>Burns, especially if affecting &gt;30% of body surface area</td>
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<td>Extreme exertion</td>
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</table>

*Modified from Jaffe et al.,*⁴ and *French and White.*⁵
Thrombus Formation and ACS

Plaque Disruption/Fissure/Erosion

→

Thrombus Formation

Old Terminology:

UA

NQMI

STE-MI

New Terminology:

Non-ST-Segment Elevation Acute Coronary Syndrome (ACS)

ST-Segment Elevation Acute Coronary Syndrome (ACS)
Characteristics of Unstable and Stable Plaque

**Unstable**
- Thin fibrous cap
- Inflammatory cells
- Few SMCs
- Eroded endothelium
- Activated macrophages

**Stable**
- Thick fibrous cap
- Lack of inflammatory cells
- More SMCs
- Intact endothelium
- Foam cells
Vulnerable plaque

1. Thin, friable fibrous caps. (cap thickness < 60 micron)
2. Thick infiltrate of macrophages (>25 per high-magnification field)
3. Lipid-rich central core (40% of its volume), with an abundant amount of lipid-laden macrophage foam cells derived from blood monocytes.
4. Blood vessels from the vasa-vasorum penetrating the plaque
5. Fractures in the internal elastic lamina
Plaque Erosion

• 30% to 40% of coronary thrombosis occurs at sites at which plaque rupture cannot be identified
• of 50 consecutive cases of sudden cardiac death attributable to coronary thrombosis, in which 22 had superficial erosion of a proteoglycan-smooth muscle cell–rich plaque (Farb. Et al).
ACS a Systemic Disease: Frequency of Multiple “Active” Plaques

80% of Patients With ≥2 Plaques


Frequency of multiple active plaque ruptures beyond the culprit lesion.
Multiple Complex Coronary Plaques in Patients with AMI

Goldstein et al. NEJM 2000
Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions

Pathogenesis of Acute Coronary Syndromes: the integral role of platelets

- Plaque Fissure or Rupture
- Platelet Adhesion
- Platelet Activation
- Platelet Aggregation
- Thrombotic Occlusion
3 Major systems involved

• Vessel wall
  – Endothelium

• Platelets

• Coagulation cascade
Endothelial Dysfunction
Anti-coagulant Properties of the Endothelium

- Endothelial cells produce t-PA which activates fibrinolysis via plasminogen to plasmin

- Heparin-like molecules (proteoglycans), which activate anti-thrombin III (inactivates thrombin, other clotting factors)

- Thrombomodulin – transmembrane proteoglycan binds thrombin – activates protein C (by cleavage) - process occurs on thrombomod. (protein C, inactivates Va & VIIIa)

- TFPI – tissue factor pathway inhibitor – released from endothelial cells (and from platelets), inhibits TF-VIIa & Xa
Superoxide-NO balance affects the vascular anti/proinflammatory phenotype

Granger, D. N. et al. Hypertension 2004;43:924-931
Isoprostanes: between inflammation and thrombosis
Vascular hemostatic and antioxidant defense mechanisms

Platelet Adhesion

• Platelets are the first cells to tether and adhere to injured vascular wall (subendothelium)

• Adhesion is mediated by vWF – a multimeric protein synthesized by both endothelial cells and megakaryocytes (stored in α granules) – present in plasma and ECM – serves as “an anchor”

• Platelet receptor – GPIb (part of the GP Ib/IX-V complex)

• Binding occurs only under high shear stress conditions!
Platelet Activation

Thienopyridines (ie, clopidogrel) only block one pathway to platelet activation.
Platelet Purinergic Receptors

Active Metabolite of Clopidogrel
Platelet Activation

- Release from alpha and dense granules
- Dense granules: ADP, serotonin
- Alpha granules: vWF, fibrinogen, fibronectin, growth factors (PDGF), PF4, factor V

- Activated platelets also synthesize (denovo) TxA2 from arachidonic acid
Platelet Aggregation

FIRM, BUT REVERSIBLE ADHESION

IRREVERSIBLE ADHESION
Platelet Aggregation

- Fibrinogen (immobilized)
- vWF (high shear)
- Collagen
- ADP
- Thrombin

GP IIb-IIIa

Fibrinogen, vWF

Fibrinogen
GP IIb/IIIa Receptor

- Mediates platelet aggregation
- Member of the integrin receptor family – can interact with both extracellular and cytoskeletal molecules
- One of the most abundant cell surface receptors (50-80,000 receptors per resting platelet, 15% of surface protein)
- Ca+ ions are critical for maintenance of both structure and function
- In the resting platelet the receptor has minimal binding affinity for ligands – fibrinogen and vWF
GP IIb/IIIa Receptor – cont.

• Upon activation of the platelet, conform. change of the receptor → high affinity ligand binding state + clustering of receptors on platelet surface

• Bidirectional signaling occurs (→ initiate numerous cellular responses)

• All ligands are characterized by the arginine-glycine-aspartate (RGD) sequence → implicated as the binding sites to the GP IIb/IIIa receptor

• Fibrinogen is a divalent ligand – each molecule can bind simultaneously to two GP IIb/IIIa receptors on adjacent platelets → cross-linking
Schematic depiction of integrin $\alpha_{\text{IIb}}\beta_3$

Both subunits composed of a short cytoplasmatic tail, a single transmembrane domain and a large extra-cell. domain that consists of a series of linked domains.

Both subunits are a product of a single gene located on chrom. 17.
Platelets and inflammation
Platelets in atherogenesis
“Classic Coagulation Cascade”

Intrinsic pathway

XIIa → Xla → IXa → Va → Xa → Prothrombin → VIIa → TF → Extrinsic Pathway

Fibrinogen → Thrombin → Fibrin → Soft clot → Hard clot

Fibrin

XIIIa
Localization to sites of vascular injury. Protease complexes assemble on PL membranes of activated platelets, endothelial cells and monocytes. (The coagulation cascade occurs very slowly in fluid phase plasma and with resting cells.)

4 major Anti-thrombotic Pathways (TFPI, Prot C/S, ATIII, Plasmin)

Rosenberg et al NEJM 1999
Current View of the Coagulation System

• Initiation by vessel wall injury which exposes blood to cells with TF on their surface → TF/FVIIa activates FX → Xa + Va cleaves II → small amounts of IIa (thrombin)

• Minute amounts of thrombin produced initially than lead to a marked increase in activation of FXI, FIX, FVIII, FV and marked generation of thrombin.

• Priming involves adherence and activation of platelets. The small amounts of initial thrombin activates platelets → release of FV + PL surface for protease activation

• Propagation – an explosive increase in thrombin generation mediated by the classic “intrinsic system” → FXI, FIX → Fxa/VIIIa/Va on activated platelets → IIa + fibrin formation

Schneider D et al, Circulation 2007
Enzymatic Amplification in the Coagulation Cascade

Initiation

Amplification

Propagation

150:1

Courtesy of Dr. N. Kleiman
Role of Platelets in Current View of the Coagulation System

- Adherence after vascular injury
- Formation of platelet-platelet aggregates (GP IIb/IIIa) and platelet-WBC aggregates (P-selectin)
- Release of platelet granule products – Ca, FV, fibrinogen
- Recruitment of additional activated platelets (ADP, TXA2)
- Stimulation of vasoconstriction (serotonin)
- Formation of thrombin promoted by PL surface on which the coagulation complexes form (priming + proagation)
- Change in shape with pseudopod extension
The Platelet as a Mediator of Coagulation

- Thrombin Generation
- Coagulation Factors
- Phosphatidyl Serine
- CD40L
- WBC
- P-Selectin
- PSGL-1
- ACTIVATED PLATELET
- Amplification Cycle
- Thrombin Generation
- Tissue Factor Expression

Courtesy of Dr. P. Gurbel
Central Role of ADP and Thrombin Crosstalk: a “Viscous” Cycle

Thrombin

PAR-1  PAR-4

PAR-1  PAR-4

Thrombin

Increased Thrombin Generation

Platelet Activation

Dense Granule Secretion

Procoagulant Platelets

ADP  P2Y_{12} (P2Y_1)

GP IIb-IIIa

Platelet Aggregation

P2Y_{12} (P2Y_1)

Courtesy of Dr. P. Gurbel
Current View of the Coagulation System

Del Conde et al CCI, 2003
The Virchow Triad of Thrombogenicity

- Local vessel wall substrates
  - Plaque components, inflammation, post-injury...
- Rheology
  - Shear stress, vasoconstrictor, bifurcation, post-intervention...
- Systemic factors of circulating blood
  - Metabolic&hormonal factors, hemostasis...

Vulnerable Plaque (Rupture-prone) ↔ Vulnerable Blood (Prone to thrombosis) ↔ Vulnerable Patient (Unstable, high-risk patient)
בצלחת, אל תעבדו קשה Midi!
шеולה 1:

מה שCJKות מחולק כל יד משולבות – לבית,
מוחית והיקפית – בקרוב חולי אטרורומבודיס?

1) פוחת מ 10% (1
2) 15-25% (2
3) 30-40% (3
4) 45-55% (4
5) מעלי 75% (5
שאלה 2:

מה המבנים הבאים מ.clsף רבד רגשי (vulnerable plaque)

1. ליבת שאומנת
2. תכולת קולגן גבוהה
3. יוזר NO נמוך, hü האנדוטל המצפפה
4. דק Fibrous cap
5. ריבי וסא-זרומים (vasa vasorum)
שאלה 3:

מבין הבאים,מי איינו תורם לתהליך הדלקתי-טרשתי (Vulnerability) הדורב התורמיולחוסר יציבות (הרובד) הטרשתי?

Vascular cell adhesion molecule-1 .1
Monocyte chemoattractant protein-1 .2
Interferon Gamma .3
Smooth muscle cells .4
T Lymphocytes .5
שאלה 4:

מי המשנים (מרקריהם) הבאים вполне קשור לחנגות הסיכון לאירועים карדיואליים וסכולרים והמותה קרדיואלית?

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<thead>
<tr>
<th>מספר</th>
<th>מרקר הstackpathים</th>
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<tbody>
<tr>
<td>1</td>
<td>IL-6</td>
</tr>
<tr>
<td>2</td>
<td>Soluble CD 40 ligand</td>
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<tr>
<td>3</td>
<td>BNP</td>
</tr>
<tr>
<td>4</td>
<td>Angiotensin type II receptor</td>
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<td>5</td>
<td>CRP</td>
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שאלה 5:

מהן השיטות הבאותапример איך ניתן להבחין ב Plaque רגיש? Vulnerable plaque של ל検测?

IVUS 1
Angioscopy 2
Thermography 3
MRI 4
Optical Coherence Tomography 5
בצלמה, אל תעבדו קשה入り!